=> file casreac
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FILE CONTENT:1840 - 5 Jul 2008 VOL 149 ISS 2

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provided by InfoChem, INPI data prior to 1986, and Biotransformations
database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance
identification.

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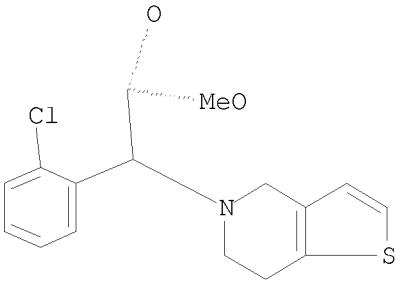
L4 STR



Structure attributes must be viewed using STN Express query preparation.
L6 40 SEA FILE=CASREACT SSS FUL L4 (736 REACTIONS)
L7 0 SEA FILE=CASREACT L6 AND HYDROGEN SULPHATE

=> d l6 1-40 ibib abs fcrd

L6 ANSWER 1 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:538244 CASREACT
TITLE: An improved process for preparing Clopidogrel bisulfate
INVENTOR(S): Gokhale, Niranjan Gangadhar; Chandrashekhar, Mahinderkar
PATENT ASSIGNEE(S): Glochem Industries Limited, India
SOURCE: Indian Pat. Appl., 19pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent

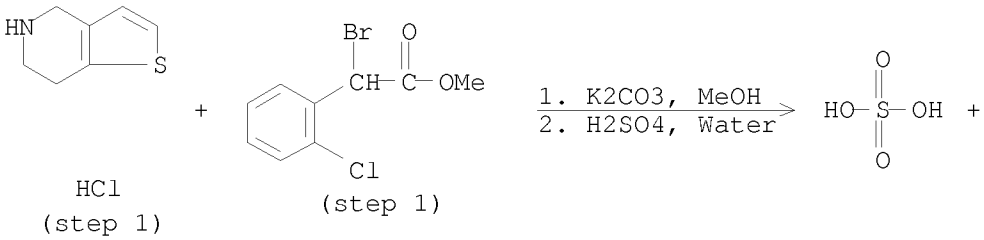
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

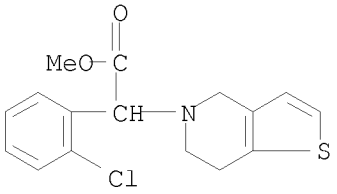
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2007CH00587	A	20070928	IN 2007-CH587	20070323

PRIORITY APPLN. INFO.: IN 2007-CH587 20070323

AB The invention relates to a process for the production of (αS)-α-(2-chlorophenyl) -6,7-dihydrothieno [3,2-c] pyridine-5(4H)-acetic acid Me ester sulfate, known as Clopidogrel bisulfate. For instance, Clopidogrel bisulfate was prepared by substitution of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prepared given) with Me α-bromo-2-chlorophenyl acetate followed by resolution using L-camphor sulfonic acid and purification

RX(2) OF 5





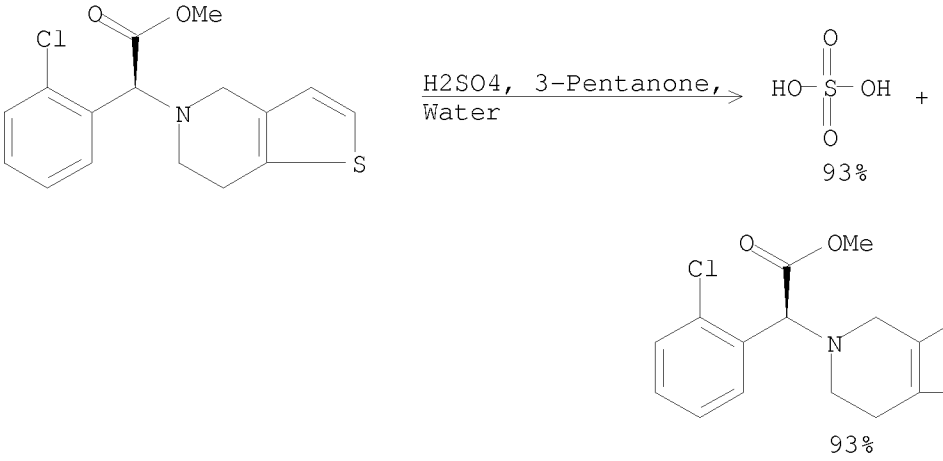
NOTE: industrial
CON: STAGE(1) 1 hour, 45 deg C; 5 - 8 hours, reflux

L6 ANSWER 2 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:285078 CASREACT
TITLE: Synthesis of crystalline forms I of clopidogrel hydrogen sulfate and mutual conversion of the crystalline forms
AUTHOR(S): Pan, Xianhua; Mao, Haifang; Lang, Xihong
CORPORATE SOURCE: School of Biotechnology and Food Processing Engineering, Shanghai Institute of Technology, Shanghai, 200235, Peop. Rep. China
SOURCE: Jingxi Huagong (2006), 23(12), 1221-1226
CODEN: JIHUFJ; ISSN: 1003-5214
PUBLISHER: Jingxi Huagong Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB A synthetic method for the production of crystalline form I of clopidogrel hydrogen sulfate (I) was improved. With 3-pentanone as solvent, a reaction at -10 to -16° for 10-16 h, gave I in 80% yield. A method for the mutual

conversion of the crystalline form I and crystalline form II of clopidogrel (II) was
also developed. I and II were characterized by m.p., FTIR spectrometry and x-ray powder diffraction.

RX(1) OF 17



NOTE: optimization study, optimized on solvent, reaction temperature, reaction time
CON: STAGE(1) room temperature -> -10 deg C; -16 - -10 deg C;
-10 deg C -> room temperature; 10 - 16 hours,
room temperature

L6 ANSWER 3 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:262485 CASREACT
TITLE: Process for preparation of (S)-(+)-clopidogrel
INVENTOR(S): Kim, Nam Ho; Lee, Jin Young; Kim, Jae-Sun; Lee, Nam Kyu
PATENT ASSIGNEE(S): SK Chemicals Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 28pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

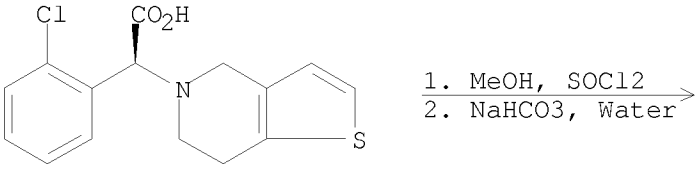
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008018779	A1	20080214	WO 2007-KR3868	20070813

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

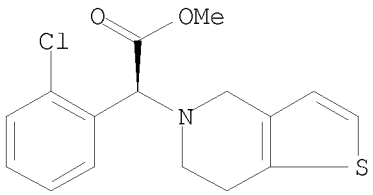
BY, KG, KZ, MD, RU, TJ, TM
KR 2008014510 A 20080214 KR 2006-76310 20060811
KR 834967 B1 20080603
PRIORITY APPLN. INFO.: KR 2006-76310 20060811

AB The present invention relates to a process for the preparation of (S)-(+)-clopidogrel in high yield by means of racemization of filtrate, and particularly to a process comprising: (a) conducting an optical resolution by converting racemic carboxylic acid of clopidogrel to a diastereomer salt using (+)-cinchonine; (b) preparing carboxylic acid of (S)-(+)-clopidogrel by extraction using an appropriate solvent under an acidic condition; (c) preparing optically pure (S)-(+)-clopidogrel by reacting the carboxylic acid of (S)-(+)-clopidogrel with methanol. The filtrate, after collecting the diastereomer salt as solid ppts. in step (a) above, is recycled after being converted to a racemic carboxylic acid of clopidogrel via racemization under a basic condition, thereby maximizing the yield of (S)-(+)-clopidogrel. The title process for the preparation of (S)-(+)-clopidogrel is advantageous both environmentally and economically.

RX(1) OF 2



(step 1)



88%

CON: STAGE(1) 6 hours, 70 deg C; 70 deg C -> room temperature
STAGE(2) room temperature, pH 7

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:121959 CASREACT
TITLE: An improved process for the preparation of clopidogrel and its pharmaceutically-acceptable salts
INVENTOR(S): Satyanarayana Reddy, Manne; Kishore Kumar, Muppa; Thirumalai Rajan, Srinivasan; Rama Subba Reddy, Karamala
PATENT ASSIGNEE(S): MSN Laboratories Limited, India
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2008004249	A2	20080110	WO 2007-IN269	20070703
WO 2008004249	A3	20080410		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

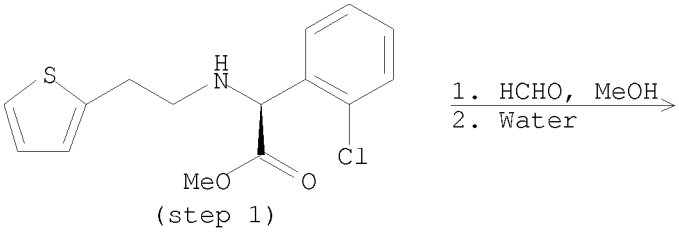
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

IN 2006CH01158	A	20080125	IN 2006-CH1158	20060704

PRIORITY APPLN. INFO.: IN 2006-CH1158 20060704

AB An improved process for the preparation of clopidogrel and its pharmaceutically-acceptable salts, especially the HCl and HBr salts, involves addition of a suitable acid to clopidogrel base in a solvent and isolation of the salts. Thus, aqueous HBr was slowly added to clopidogrel base dissolved in cyclohexane and the mixture stirred for 14 h at 25-35°C. The filtered precipitated solid was washed with a mixture of cyclohexane and iso-Pr alc. and dried to afford clopidogrel hydrobromide having a plate morphol. Clopidogrel was prepared by treating (S)-Me [[2-(thiophen-2-yl)ethyl]amino](2-chlorophenyl)acetate with formalin methanol solution in the presence of p-toluenesulfonic acid at 50-55°C for 28 h.

RX(1) OF 4



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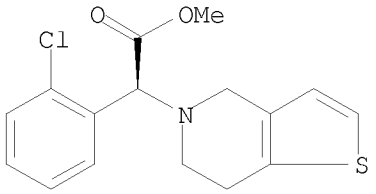


CON: STAGE(1) 20 - 25 deg C; 25 deg C -> 55 deg C; 28 hours, 50 - 55 deg C; 55 deg C -> 25 deg C

L6 ANSWER 5 OF 40 CASREACT COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	148:55031 CASREACT
TITLE:	An improved process for the preparation of Clopidogrel
INVENTOR(S):	Ramasubbu, Chandrasekaran; Mamidala, Rajanikanth; Arjunan, Desinghu; Ramasamy, Karthik; Siripragada, Mahender Rao
PATENT ASSIGNEE(S):	Orchid Chemicals & Pharmaceuticals, Limited, India
SOURCE:	PCT Int. Appl., 14pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007144729	A1	20071221	WO 2007-IB1542	20070608
IN 2006CH01018	A	20080425	IN 2006-CH1018	20060613

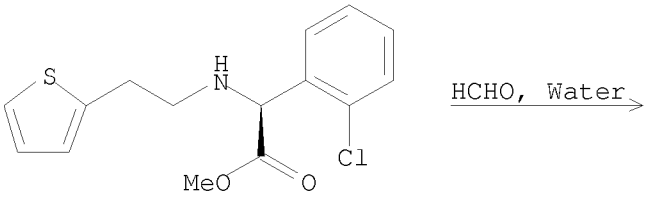
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: IN 2006-CH1018 20060613

AB The present invention relates to an improved process for the preparation of Clopidogrel, Me (2S)-(2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate. More particularly, the present invention relates to an improved process for the preparation of Clopidogrel intermediate, Me (2S)-(+)-(2-chlorophenyl)-N-[2-(2-thienyl)ethyl]glycinate or its salt, using triethylamine as an organic base in the absence of an organic solvent.

RX(3) OF 8



63%

CON: STAGE(1) room temperature -> 60 deg C; 20 - 30 minutes, 60 deg C

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:55030 CASREACT
TITLE: Preparation of (S)-(+)-clopidogrel

INVENTOR(S): Dholakia, Parind Narendra; Dave, Mayank Ghanshyambhai; Pandey, Bipin; Lohray, Braj Bhushan; Lohray, Vidya Bhushan; Patel, Pankaj Ramanbhai
PATENT ASSIGNEE(S): Cadila Healthcare Limited, India
SOURCE: PCT Int. Appl., 11pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007144895	A1	20071221	WO 2006-IN465	20061120

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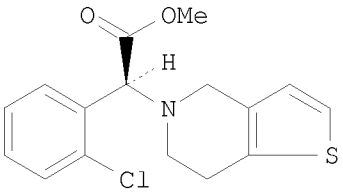
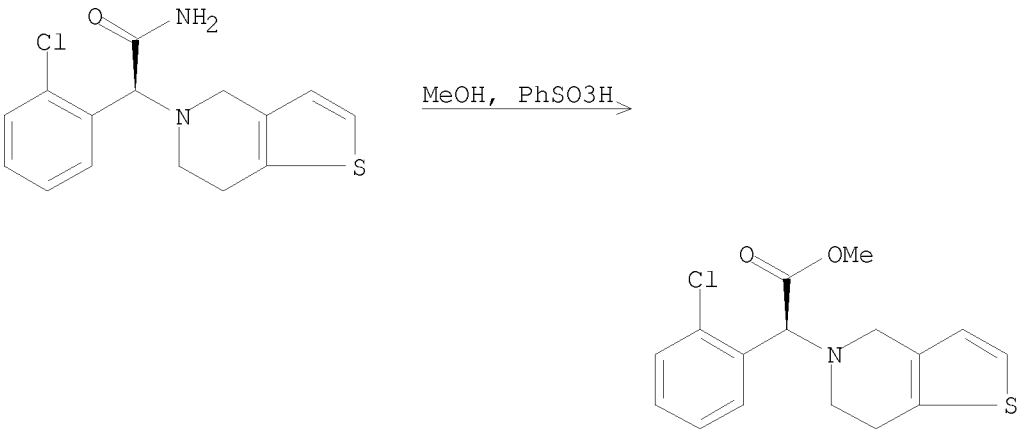
PRIORITY APPLN. INFO.: IN 2006-MU914 20060612
GI



I

AB A process for the preparation of Me (+)-(S)-clopidgrel (I) is disclosed. The process comprises a) contacting a carboxamide with sulfonic acid(s) such as benzene- or methanesulfonic acid and methanol; b) refluxing or heating the reaction mixture to elevated temperature for 2-40 h; c) basifying the salt using suitable base(s) and evaporating the solvent.

RX(1) OF 1



NOTE: Alternative preparations shown
CON: 10 - 24 hours, reflux

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:469318 CASREACT
TITLE: Process for preparation of (S)-clopidogrel and its salts
INVENTOR(S): Ye, Chenghai
PATENT ASSIGNEE(S): Shenzhen Salubris Pharmaceuticals Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 13pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

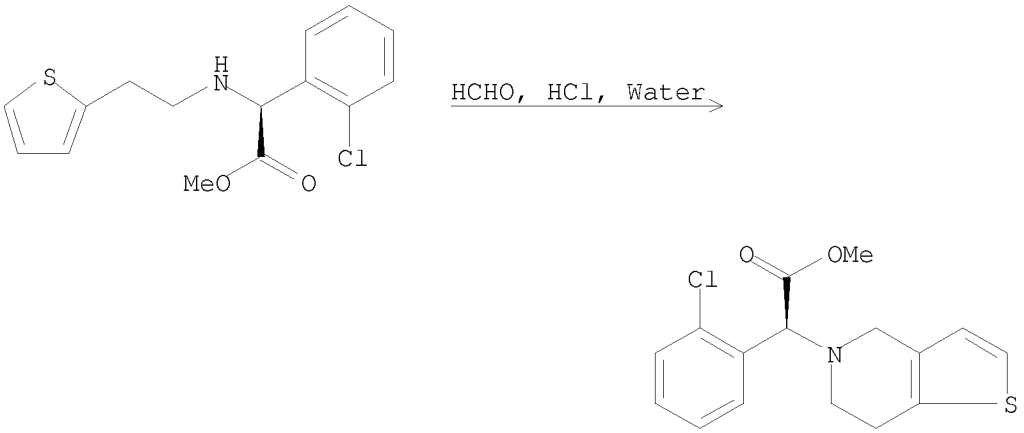
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101045731	A	20071003	CN 2006-10062880	20060929

PRIORITY APPLN. INFO.: CN 2006-10062880 20060929

AB The title method comprises the steps of: (1) dissolving racemic Me α-(2-(2-thienyl)ethylamino)-α-(2-chlorophenyl)acetate (I) hydrochloride in water, adding dichloromethane, stirring, adjusting pH value with sodium bicarbonate or potassium bicarbonate to 7-8 to form two layers, combining organic phase, washing organic phase with water, drying the organic phase with anhydrous sodium sulfate or potassium sulfate, and vacuum-distilling to obtain oily substance, (2) dissolving the oily substance obtained in step 1 in 2-propanol, adding L-tartaric acid, heating to 45-55° with stirring, keeping temperature for 0.5 h, slowly cooling to 30-40°, adding crystal seed, stirring overnight at room temperature, cooling to 15-20°, stirring for 4 h, vacuum-filtering solid, washing, and drying to obtain L-tartaric acid salt of (+)-I , (3) vacuum-distilling the mother liquid after vacuum-filtering to obtain residue, performing treatment of residue according to step 1 procedure to obtain product, dissolving the above product with anhydrous methanol, dropping sodium methoxide in ice bath, slowly heating to room temperature, and stirring

overnight, (4) dropping concentrated sulfuric acid to the mixed solution obtained
in step 3 in ice bath, refluxing for 6 h, immediately pouring the reaction solution into ice-water, adding dichloromethane, repeating step 1 to obtain product, dissolving the above product with Et acetate, dropping concentrated hydrochloric acid in ice bath to form salt. Treatment of L-tartaric acid salt of (+)-I with aqueous NaHCO3, followed by the reaction with formaldehyde to give (S)-clopidogrel. This method has the advantages of simple reaction route, short cycle period, low cost and high product purity, and also can decrease reaction toxicity and equipment corrosion by using sulfuric acid to replace thionyl chloride.

RX(1) OF 21



CON: STAGE(1) room temperature -> 80 deg C; 2 hours, 70 - 80 deg C;
80 deg C -> 5 deg C; 0 - 5 deg C

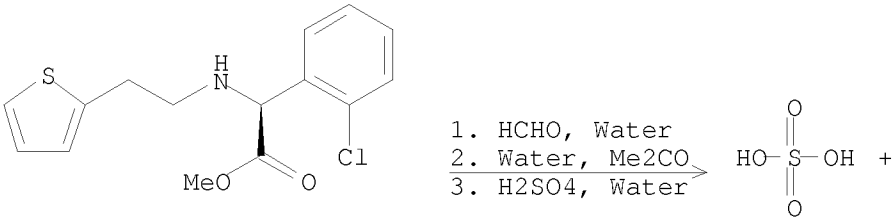
L6 ANSWER 8 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:406804 CASREACT
TITLE: Process for preparing clopidogrel or salt thereof
INVENTOR(S): Sajja, Eswaraiah; Anumula, Raghupathi Reddy; Gilla, Goverdhan; Madivada, Lokeswara Rao
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 10pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070225320	A1	20070927	US 2007-691295	20070326
IN 2006CH00545	A	20071207	IN 2006-CH545	20060327
PRIORITY APPLN. INFO.:			IN 2006-CH545	20060327
			US 2006-807783P	20060719

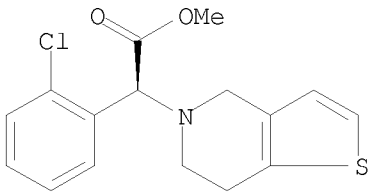
AB This document discloses a process for preparing clopidogrel or a salt thereof comprising reacting racemic Me α-amino-(2-chlorophenyl)acetate with L-(+)-tartaric acid , separating the tartaric acid salt of (S)-(+)-Me α-amino-(2-chlorophenyl)acetate from the reaction mixture, and heating a reaction mixture to form racemic Me α-amino-(2-chlorophenyl)acetate (I), reacting I with L-(+)-tartaric acid to form the tartaric acid salt of

(S)-(+)-Me α-amino-(2-chlorophenyl)acetate. Thus, α-amino-(2-chlorophenyl)acetic acid Me ester (II) 140 kg in methanol 1485 L was treated with L-(+)-tartaric acid 105 kg to give the L-(+)-tartaric acid salt (81 kg) of the (S)-(+)-isomer of II : this salt was treated with aqueous sodium bicarbonate solution to give the (S)-(+)-isomer of II; clopidogrel bisulfate was prepared from the (S)-(+)-isomer of II in 3 steps.

RX(5) OF 18



HCl
(step 1)



CON: STAGE(1) 24 hours, 30 deg C -> 25 deg C
STAGE(2) room temperature -> 0 deg C
STAGE(3) 3.75 hours, 0 deg C; 10 minutes, 0 deg C

L6 ANSWER 9 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:263254 CASREACT
TITLE: Process for preparation of clopidogrel bisulfate Form-1
INVENTOR(S): Alla, Venkat Reddy; Vyakaranam, Kameshwara Rao; Sirigiri, Aruna Kumari; Bodapati, Srinivas Reddy; Billa, Ranadheer Reddy; Gudibandi, Saikrishna Reddy; Alla, Raghumitra
PATENT ASSIGNEE(S): Lee Pharma Limited, India
SOURCE: U.S. Pat. Appl. Publ., 6pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070191609	A1	20070816	US 2006-307663	20060216
IN 2006CH00223	A	20071123	IN 2006-CH223	20060213
WO 2007094006	A1	20070823	WO 2006-IN117	20060405

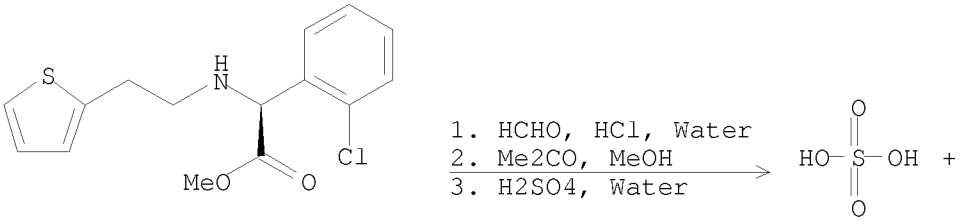
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: IN 2006-CH223 20060213

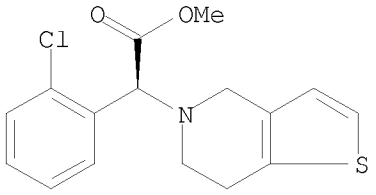
AB Disclosed herein is a cost effective and industrially feasible process for the preparation of (+)-clopidogrel bisulfate. The present invention further discloses a novel method of precipitation of (+)-clopidogrel bisulfate Form I directly from solvent mix of methanol and acetone in the presence of sulfuric acid at a temperature of 25-40°.

RX(5) OF 15



HCl

(step 1)



NOTE: paraformaldehyde used (first stage)

CON: STAGE(1) 1 hour, room temperature -> 85 deg C;
85 deg C -> 25 deg C
STAGE(2) room temperature -> 5 deg C
STAGE(3) 3 hours, 0 - 5 deg C; 12 hours, 5 deg C -> 30 deg C

L6 ANSWER 10 OF 40 CASREACT COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 147:257751 CASREACT

TITLE: Process for preparation of clopidogrel and its salt

INVENTOR(S): Ye, Chenghai

PATENT ASSIGNEE(S): Shenzhen Salubris Pharmaceuticals Co., Ltd., Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 12pp.
CODEN: CNXXEV

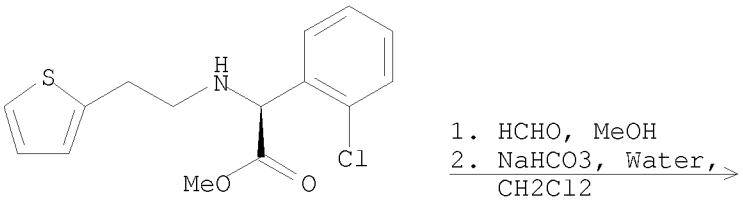
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 100999525	A	20070718	CN 2006-10063152	20061018

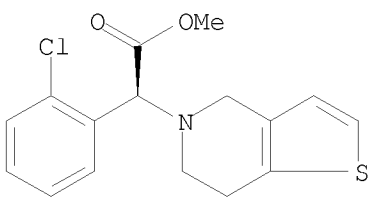
PRIORITY APPLN. INFO.: CN 2006-10063152 20061018

AB The title method comprises the steps of: (1) dissolving racemic Me o-chlorophenylglycinate hydrochloride in water, adding dichloromethane, adjusting pH value to 7-8 with sodium hydrogen carbonate and/or potassium hydrogen carbonate under stirring, separating to obtain organic phase, washing with water, drying with anhydrous sodium sulfate and/or potassium sulfate, and vacuum-drying to obtain Me o-chlorophenylglycinate, (2) dissolving with isopropanol, adding L-tartaric acid, stirring for 30 min, adding a crystal seed, stirring at normal temperature for over night, cooling to 15-20 °C, stirring for 4 h, vacuum-filtrating, and drying to obtain tartrate of Me (S)-o-chlorophenylglycinate, (3) vacuum-evaporating the filtrate obtained in step 2, treating by the process of step 1, dissolving with methanol, placing into an ice bath, dropping sodium methoxide solution, heating naturally, and stirring at normal temperature for over night, (4) placing the crystals obtained in step 2 into the ice bath, dropping concentrated sulfuric acid, refluxing for 4 h, adding into ice water, adding dichloromethane, treating by the process of step 1, dissolving with acetone, placing in the ice bath, dropping concentrated hydrochloric acid, vacuum-filtrating to obtain solid phase, washing with cold acetone, and drying to obtain hydrochloride of Me (S)-o-chlorophenylglycinate, (5) repeating steps 1-4, and (6) preparing clopidogrel with obtained tartrate of Me (S)-o-chlorophenylglycinate. This invention has easy process flow, short circulation period, low cost, low toxicity and corrosion, and high product purity.

RX(5) OF 21



HCl
(step 1)



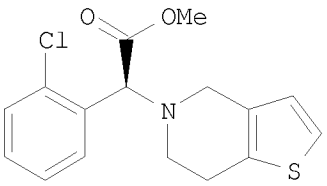
CON: STAGE(1) 3 - 4 hours, 55 deg C; 55 deg C -> 30 deg C
STAGE(2) 30 deg C, pH 7 - 8

L6 ANSWER 11 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:166306 CASREACT
TITLE: Process for preparing clopidogrel
INVENTOR(S): Hajicek, Josef; Pihera, Pavel; Stepankova, Hana
PATENT ASSIGNEE(S): Zentiva, A. S, Czech Rep.
SOURCE: Czech Rep., 11 pp.
CODEN: CZXXED
DOCUMENT TYPE: Patent
LANGUAGE: Czech
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

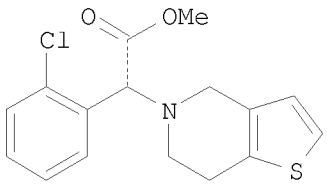
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CZ 295920	B6	20051116	CZ 2004-1048	20041018
WO 2006042481	A1	20060427	WO 2005-CZ77	20051017

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: CZ 2004-1048 20041018
OTHER SOURCE(S): MARPAT 147:166306
GI



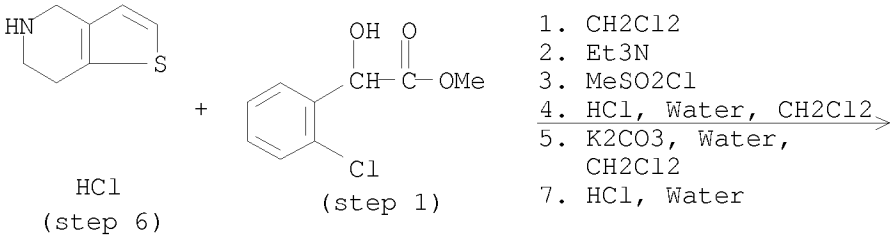
I

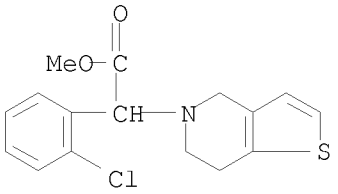


II

AB The title compound I is obtained from its racemic mixture or its enantiomer-enriched mixture with its R isomer II by crystallization of salts of I and II with R(-)-10-camphorsulfonic acid (III) followed by isolation of I in such a way that crystallization is conducted in one or several steps using a mixture of at least two solvents. At least one of the solvents, having a mol. formula RaOH where Ra is a linear or branched C1-C5 alkyl, is a good solvent for III and its salts with I and II. The other component(s) of the solvent system are not good solvents for III and its salts, but are good solvents for both I and II.

RX(1) OF 2





70%

CON: STAGE(1) room temperature
STAGE(2) room temperature -> 10 deg C
STAGE(3) 1 hour, 10 - 15 deg C
STAGE(4) room temperature
STAGE(5) room temperature
STAGE(6) room temperature -> reflux; 20.5 hours, reflux; reflux -> room temperature
STAGE(7) room temperature

L6 ANSWER 12 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:143403 CASREACT
TITLE: Process for the preparation of (S)-(+)-clopidogrel by optical resolution
INVENTOR(S): Kim, Nam Ho; Lee, Jin Young; Kim, Jae-Sun; Lee, Nam Kyu
PATENT ASSIGNEE(S): Sk Chemicals Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007074995	A1	20070705	WO 2006-KR5600	20061220

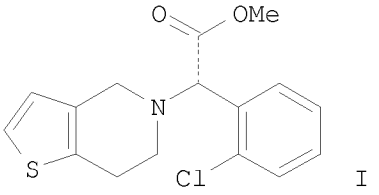
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,

CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

KR 2007068043 A 20070629 KR 2005-129717 20051226

PRIORITY APPLN. INFO.: KR 2005-129717 20051226

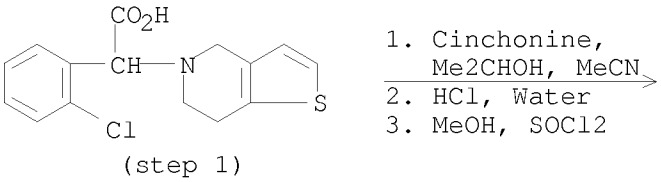
GI



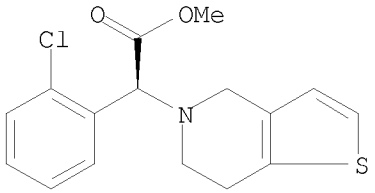
I

AB The present invention relates to a process for the preparation of (S)-(+)-clopidogrel by an optical resolution and, more particularly, to a process for the preparation of (S)-(+)-clopidogrel represented by the formula I with high optical purity by converting a clopidogrel racemic carboxylic acid into a diastereomeric salt using a (+)-cinchonine for optical resolution, extracting an (S)-(+)-clopidogrel carboxylic acid from the diastereomeric salt using a suitable solvent under an acidic conditions, and then reacting the (S)-(+)-clopidogrel carboxylic acid with methanol.

RX(1) OF 1



(step 1)



NOTE: Resolution, stereoselective
CON: STAGE(1) 18 hours, room temperature
STAGE(2) room temperature, pH 4
STAGE(3) room temperature; 6 hours, 70 deg C

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:118231 CASREACT
TITLE: Process for the preparation of (S)-(+)-clopidogrel on a solid-phase
INVENTOR(S): Lee, Jin Young; Kim, Nam Ho; Kim, Jae-Sun; Lee, Nam Kyu
PATENT ASSIGNEE(S): SK Chemicals Co., Ltd., S. Korea

SOURCE: PCT Int. Appl., 29pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

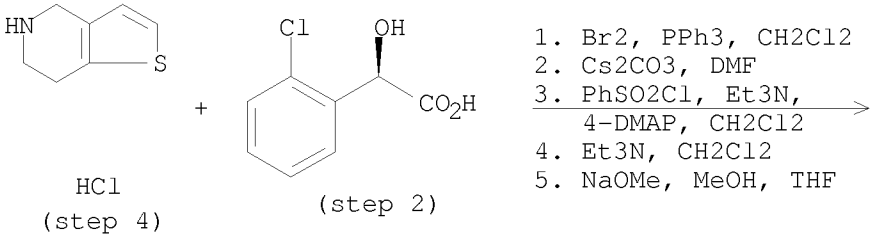
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007073095	A1	20070628	WO 2006-KR5602	20061220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
KR 2007066518	A	20070627	KR 2005-127800	20051222

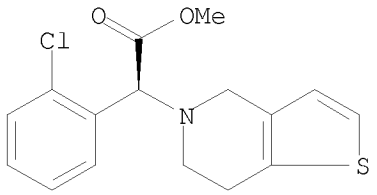
PRIORITY APPLN. INFO.: KR 2005-127800 20051222
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for solid phase synthesis of an S-(+)-clopidogrel comprising the preparation of sulfonylated resin (I) (R1 = SO2Ph; R2 = polymer support for solid-phase reaction) by sulfonylating a hydroxy resin I (R1 = H; R2 = polymer support for solid-phase reaction), following by preparation of resin compound (II) by reacting the sulfonylated resin I (R1 = SO2Ph; R2 = polymer support for solid-phase reaction) with 4,5,6,7-tetrahydro[3,2-c]thienopyridine hydrochloride and separation of the S-(+)-clopidogrel (III) from the polymer support by Me esterification is developed. Resin I (R1 = H; R2 = polymer support for solid-phase reaction) was prepared by bromination of Wang resin to form a brominated resin and then subjected to a bonding reaction with (R)-2-chloromandelic acid or by direct bonding of I (R1 = H; R2 = polymer support for solid-phase reaction) with (R)-2-chloromandelic acid. Thus, S-(+)-clopidogrel was prepared by successive solid-phase reactions starting from Wang resin according to described method in 84% yield with 98% e.e optical purity.

RX(1) OF 4





58%

NOTE: First stage attachment to Wang resin, Cleavage from resin last stage, solid-supported reaction, stereoselective
CON: STAGE(1) 10 minutes, room temperature; room temperature; 5 hours, room temperature
STAGE(2) 4 hours, room temperature
STAGE(3) room temperature; 12 hours, room temperature
STAGE(4) room temperature; 30 minutes, room temperature; 12 hours, room temperature
STAGE(5) room temperature; 6 hours, reflux

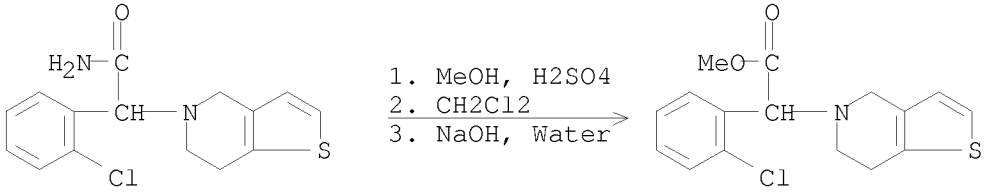
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 147:95650 CASREACT
TITLE: Process for the preparation of (2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetonitrile derivatives as clopidogrel synthons from 4,5,6,7-tetrahydrothieno[3,2-c]pyridine via condensation reaction
INVENTOR(S): Barkoczy, Jozsef; Kotay Nagy, Peter; Simig, Gyula; Gregor, Tamas; Nagy, Kalman; Vereczkeyne, Donath Gyoergyi; Seres, Peter; Slegel, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Hung. Pat. Appl., 15pp.
CODEN: HUXXCV
DOCUMENT TYPE: Patent
LANGUAGE: Hungarian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
HU 2000004116	A2	20020729	HU 2000-4116	20001020
HU 226038	B1	20080328		
PRIORITY APPLN. INFO.:			HU 2000-4116	20001020

AB (2-Chloro-phenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetonitrile (I) was prepared in 94% yield by condensation of 4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine hydrochloride with 2-chlorobenzaldehyde and sodium cyanide. I is a valuable pharmaceutical synthon of clopidogrel, an antithrombotic medication, which inhibits platelet aggregation.

RX(3) OF 9



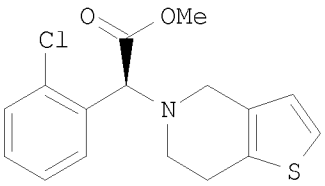
(step 1) 74%

CON: STAGE(1) 80 - 120 hours, room temperature
STAGE(2) room temperature
STAGE(3) room temperature

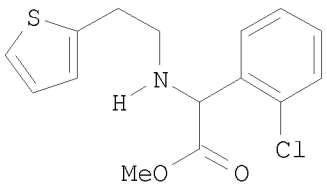
L6 ANSWER 15 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:441665 CASREACT
TITLE: Preparation of clopidogrel
INVENTOR(S): Bhushan, Lohray Vidya; Bhushan, Lohray Braj; Bipin, Pandey
PATENT ASSIGNEE(S): Zydus Research Center, Cadila Health Care Ltd., India
SOURCE: Indian, 33pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 193668	A1	20040731	IN 2001-MU335	20010411
IN 2003MU01007	A	20050715	IN 2003-MU1007	20030924
IN 2003MU01008	A	20050715	IN 2003-MU1008	20030924

PRIORITY APPLN. INFO.: IN 2001-MU335 20010411
GI



I

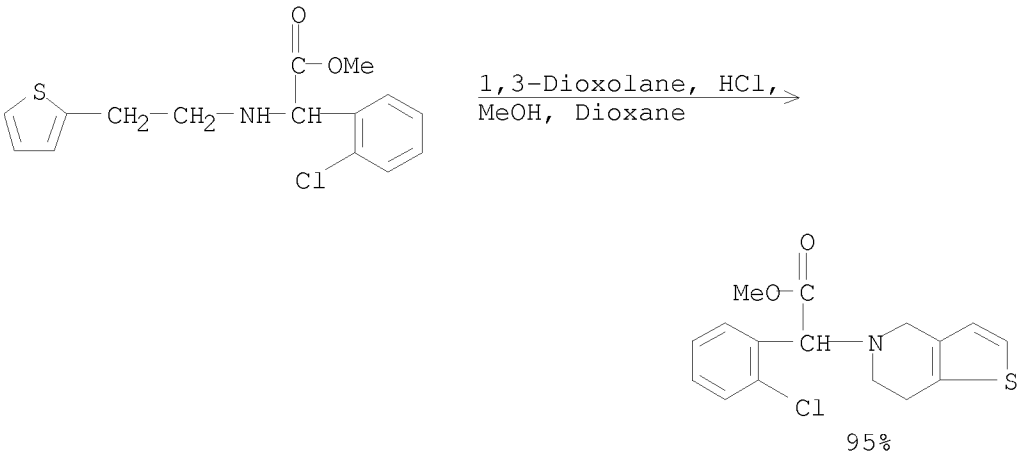


II

AB A process for the preparation of title compound I and its pharmaceutically acceptable salts was disclosed. For example, 1,3-dioxalane/HCL mediated

cyclization of amine II hydrochloride afforded the racemate of clopidogrel in 95% yield.

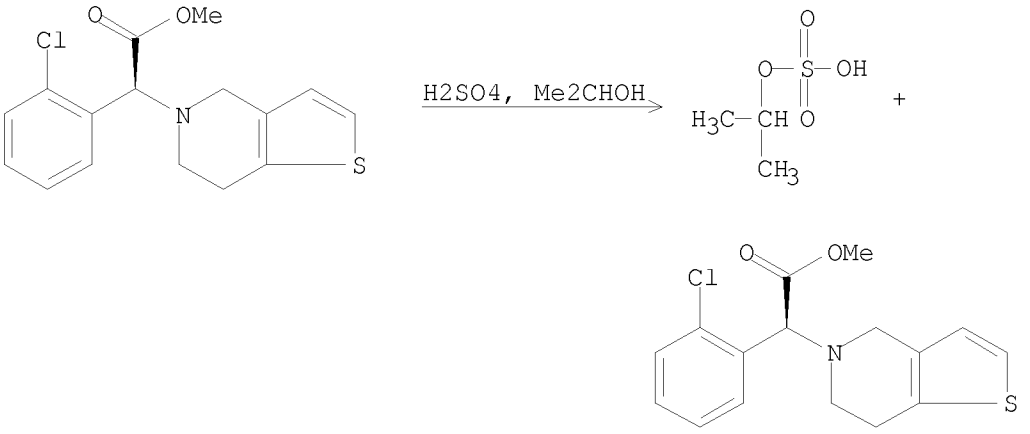
RX(8) OF 33



CON: 6 hours, 65 deg C

L6 ANSWER 16 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:391174 CASREACT
TITLE: Synthesis and x-ray structural studies of the dextro-rotatory enantiomer of methyl α-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate isopropylsulfate
AUTHOR(S): Renou, Ludovic; Coste, Servane; Coquerel, Gerard
CORPORATE SOURCE: Laboratoire des sciences et methodes separatives, UPRES EA 3233, IRCOF, Universite de Rouen, Mont-Saint Aignan, 76821, Fr.
SOURCE: Journal of Molecular Structure (2007), 827(1-3), 108-113
CODEN: JMOSB4; ISSN: 0022-2860
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study resolves conflicting data on a particular salt of the enantiomer of Me α-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)acetate ((S)-(+)-clopidogrel). The title compound, (C16H17ClNO2S)+ (i-PrO4S)-, was obtained and characterized by x-ray diffraction, NMR, TG/DSC/MS. This salt previously reported in the literature as a isoPrOH solvate of the hydrogensulfate salt appears to be actually an isopropylsulfate salt.

RX(1) OF 1



CON: STAGE(1) 90 minutes, reflux; reflux -> room temperature

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:337872 CASREACT
TITLE: Process for preparation of methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (clopidogrel) via cyclocondensation of methyl (+)-α-(2-thienylethylamino)-N-(2-chlorophenyl)acetate salt with paraformaldehyde in the presence of catalytic hydrochloric acid.
INVENTOR(S): Srivastava, Anita Ranjan; Pawar, Prashant Pandurang; Poojari, Krishna Anand; Patil, Pravin Chaitram; Dalvi, Rajiv Ramchandra
PATENT ASSIGNEE(S): RPG Life Sciences Limited, India
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007032023	A2	20070322	WO 2006-IN250	20060707
WO 2007032023	A3	20070712		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

EP 1902058 A2 20080326 EP 2006-832291 20060707
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR
PRIORITY APPLN. INFO.: IN 2005-MU836 20050709
WO 2006-IN250 20060707

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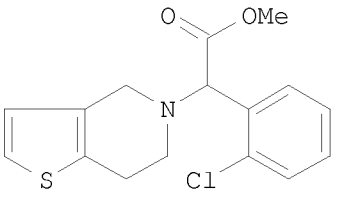

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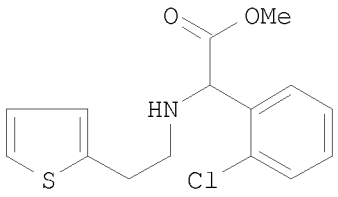
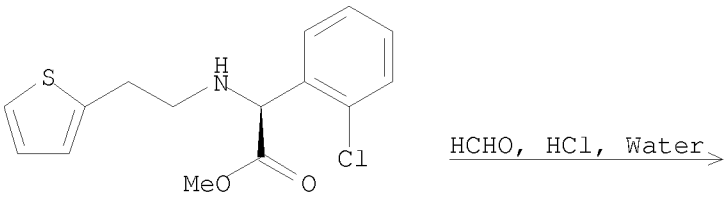


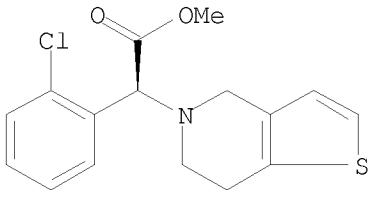
II

AB A process for preparation of clopidogrel (I) comprises reaction of Me (S)-α-(2-thienylethylamino)-N-(2-chlorophenyl)acetate (II) salt with H2CO in H2O in the presence of catalytic hydrochloric acid under heating followed by separation of the aqueous layer from the sticky mass, extraction of the aqueous layer with petroleum ether or hexane at pH 2-3, and concentration of the organic layer. Thus, II.HCl, H2CO, and cat. HCl were heated together in H2O at 78-80° for 2 h; the aqueous layer was separated and extracted twice with petroleum ether to give after concentration 83.57% I of 99.90% purity.

RX(1) OF 1



HCl



84%

NOTE: alternative preparation shown, paraformaldehyde used
CON: 2 hours, room temperature -> 80 deg C

L6 ANSWER 18 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:337870 CASREACT
TITLE: Process for preparation of clopidogrel and analogues
INVENTOR(S): Wang, Lixin; Tang, Yi; Cheng, Yi; Tian, Fang

PATENT ASSIGNEE(S): Zhejiang Huahai Pharmaceutical Co., Ltd., Peop. Rep. China; Chengdu Organic Chemicals Co., Ltd., Chinese Academy of Sciences
SOURCE: PCT Int. Appl., 73pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007028337	A1	20070315	WO 2006-CN2316	20060907
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CN 1927863	A	20070314	CN 2005-10060719	20050908
CN 1927864	A	20070314	CN 2005-10060720	20050908
CN 1927865	A	20070314	CN 2005-10060721	20050908
CN 1927866	A	20070314	CN 2005-10060722	20050908
CN 1951940	A	20070425	CN 2005-10061230	20051021
CN 1951941	A	20070425	CN 2005-10061231	20051021

PRIORITY APPLN. INFO.: CN 2005-10060719 20050908
CN 2005-10060720 20050908
CN 2005-10060721 20050908
CN 2005-10060722 20050908
CN 2005-10061230 20051021
CN 2005-10061231 20051021
OTHER SOURCE(S): MARPAT 146:337870
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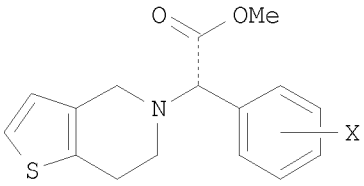
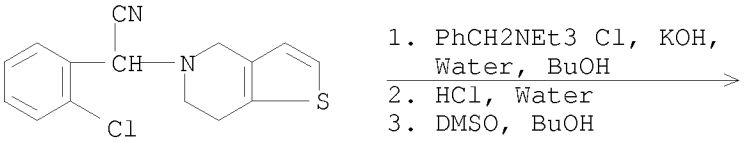


I

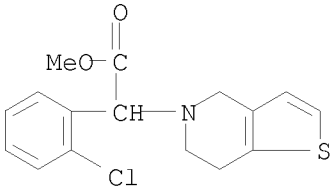
AB This invention provides a process for preparing optically active clopidogrel and its analogs I [wherein X = H, F, Cl, Br, or I] comprising kinetic resolution of racemates. For example, racemic 2-chlorophenyl-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (preparation given) was methylated with di-Me sulfate in the presence of potassium hydroxide and triethylbenzylammonium chloride to give racemic clopidogrel. The obtained racemic clopidogrel was reacted with D-camphorsulfonic acid to give (S)-clopidogrel salt with high purity. The (R)-clopidogrel can be recycled by racemization in aqueous solution in the presence of base and phase

transfer catalyst.

RX(1) OF 548



(step 1)

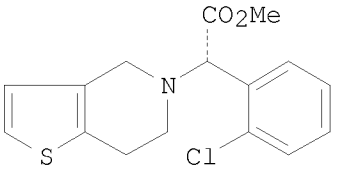


40%

NOTE: green chemistry, phase transfer catalyst used
CON: STAGE(1) room temperature -> 115 deg C; 8 hours, 115 deg C;
115 deg C -> room temperature
STAGE(2) room temperature, pH 11; room temperature, pH 9
STAGE(3) 0.5 hours, room temperature; 2 hours, room temperature,
pH 9; room temperature -> 45 deg C; >8 hours, 45 deg C;
2 hours, reflux; cooled

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:274247 CASREACT
TITLE: Process for preparation of (+)-clopidogrel hydrogen sulfate
AUTHOR(S): Balicki, Roman
CORPORATE SOURCE: Inst. Farm., Warsaw, 01-793, Pol.
SOURCE: Przemysl Chemiczny (2006), 85(5), 342-343
CODEN: PRCHAB; ISSN: 0033-2496
PUBLISHER: Wydawnictwo SIGMA-NOT
DOCUMENT TYPE: Journal
LANGUAGE: Polish
GI



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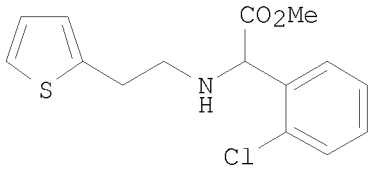
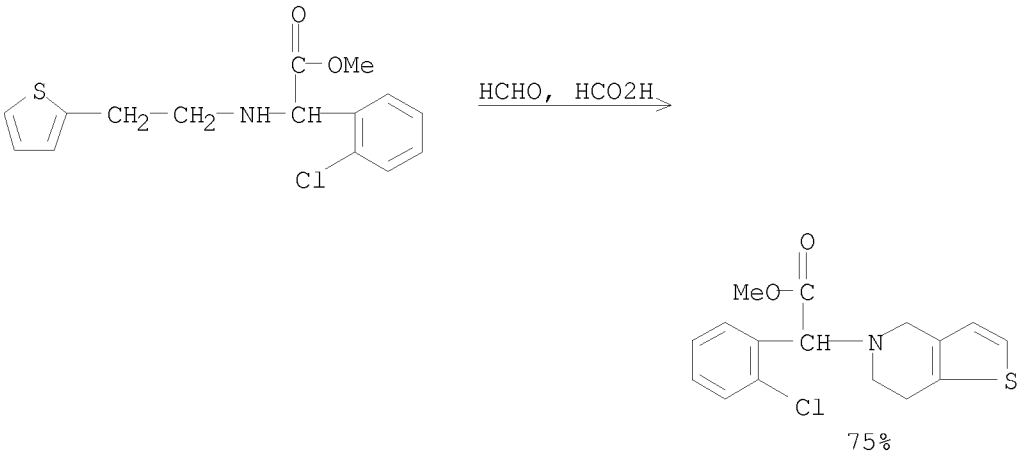


II

AB The title compound (I·H2SO4) was prepared in 3 steps from amino ester II; the desired enantiomer was separated using (-)-camphorsulfonic acid. II was prepared via a convergent route starting from 2-chlorobenzaldehyde and 2-thiopheneethanol.

RX(5) OF 24



NOTE: paraformaldehyde used

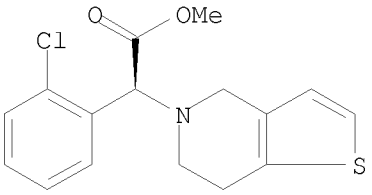
L6 ANSWER 20 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 145:454927 CASREACT
TITLE: Method for manufacturing (+)-(s-)-clopidogrel bisulfate (I type) with high purity and yield
INVENTOR(S): Zhang, Qunhui; Zheng, Zhiguo; Chen, Shaoting; Qian, Shaojian; Hu, Hefei
PATENT ASSIGNEE(S): Zhejiang Hisoar Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 17pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1850827	A	20061025	CN 2006-10051684	20060526

PRIORITY APPLN. INFO.: CN 2006-10051684 20060526

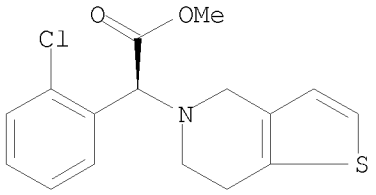
AB The title method comprises adding free alkaline of (+)-(S-)-clopidogrel (formula I) to organic solvent, dripping 10-100% sulfuric acid solution at 6-20° to the above solution, keeping at 50-65° for reaction for 10 min-1.5 h, and filtering to obtain compound represented by formula II, wherein the sulfuric acid solution is prepared by dissolving sulfuric acid in organic solvent, and organic solvent is one or mixture of Et formate, Me acetate, Et acetate, Bu acetate, Et ether, iso-Pr ether, tert-Bu Me ether, or dichloromethane. The mol. ratio of free alkaline of (+)-(S-)-clopidogrel to sulfuric acid is 1 : (0.95-1.05).

RX(1) OF 3



NaHCO3, Water, CH2Cl2

HCl

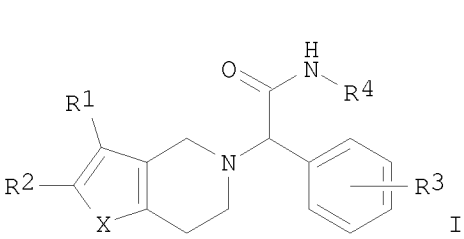


NOTE: alternate reagent described
CON: STAGE(1) room temperature; 30 minutes, room temperature;
10 minutes, room temperature

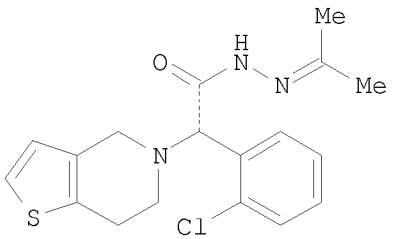
L6 ANSWER 21 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 145:62869 CASREACT
TITLE: Preparation of thieno[3,2-c]pyridine derivatives as platelet aggregation inhibitors
INVENTOR(S): Liu, Dengke; Wang, Pingbao; Zhao, Zhuanyou; Jiang, Qingfeng; Yan, Fangfang; Huang, Hanzhong; Xi, Wengong; Xu, Xu; Liu, Mo; Huang, Changjiang; Ren, Rong
PATENT ASSIGNEE(S): Tianjin Medicine Inst., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 27 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1683373	A	20051019	CN 2005-10016205	20050223

PRIORITY APPLN. INFO.: CN 2005-10016205 20050223
OTHER SOURCE(S): MARPAT 145:62869
GI



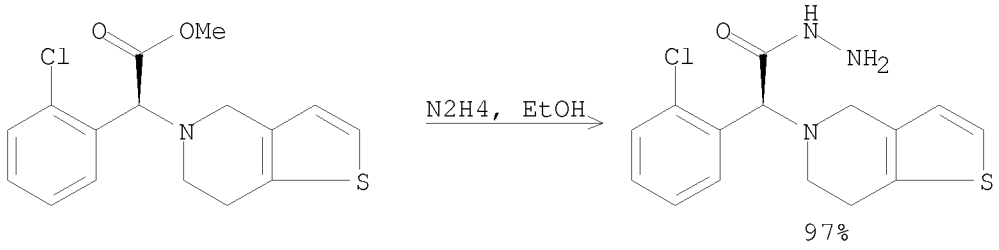
I



II

AB The title thieno[3,2-c]pyridine derivs. I [wherein X = O or S; R1 and R2 = independently H, F, Cl, NO2, or (un)substituted alkyl; R3 = H, F, Cl, NO2, CN, (un)substituted alkyl, or alkoxy; R4 = -N=R5, (un)substituted NH2, or -N=CH2; R5 = (un)substituted (hetero)cycloalkyl] or pharmaceutically acceptable salts thereof as platelet aggregation inhibitors. For example, clopidogrel was reacted with hydrazine hydrate, followed by the addition of acetone to give II. II inhibited 42.2% of platelet aggregation. Formulations as capsules, tablets, injectable liquid, and powder were described. The title compds. are useful for preventing and treating platelet aggregation caused coronary artery syndromes, myocardial infarction, myocardial ischemia, cardiac, and cerebral vascular diseases (no data).

RX(1) OF 52



97%

CON: STAGE(1) room temperature -> reflux; 4 hours, reflux

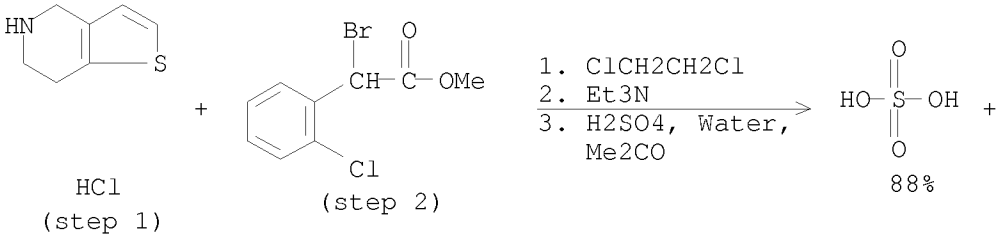
L6 ANSWER 22 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 143:440758 CASREACT
TITLE: Industrial process for preparation of clopidogrel hydrogen sulfate
INVENTOR(S): Kumar, Ashok; Vyas, Ketan Dhansukhlal; Barve, Sanjay Govind; Bhayani, Priti Jayesh; Nandavadekar, Sanjay; Shah, Chirag Hasmukh; Burudkar, Sandeep Madhavrao; Kushwaha, Lavkesh Dayashankar
PATENT ASSIGNEE(S): Ipca Laboratories Limited, India
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

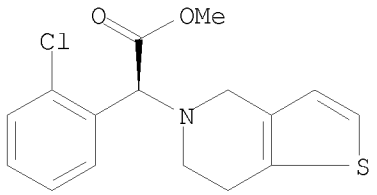
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2005104663 A2 20051110 WO 2005-IN71 20050304
WO 2005104663 A3 20060928
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
IN 2004MU00281 A 20060616 IN 2004-MU281 20040305
IN 2004MU00626 A 20061027 IN 2004-MU626 20040604
IN 2004MU00861 A 20070608 IN 2004-MU861 20040810
EP 1723141 A2 20061122 EP 2005-767878 20050304
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU
EP 1772455 A2 20070411 EP 2006-120928 20050304
EP 1772455 A3 20070627
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU
US 20080097101 A1 20080424 US 2006-591657 20060905
PRIORITY APPLN. INFO.: IN 2004-MU281 20040305
IN 2004-MU626 20040604
IN 2004-MU861 20040810
EP 2005-767878 20050304
WO 2005-IN71 20050304
OTHER SOURCE(S): MARPAT 143:440758

AB An industrial process for manufacture of clopidogrel comprises one-pot conversion of 2-(2-thienyl)ethylamine by the action of paraformaldehyde and an acid catalyst into 4,5,6,7-tetrahydrothieno(3,2-c)pyridine intermediate [without isolation of 2-(2-thienyl)ethylformimine], which reacts with Me bromo- or chloro(2-chlorophenyl)acetate in the presence of a base in CH_2Cl_2, water or aqueous hydrocarbon/chlorinated hydrocarbon solvents at 20-90 °C. Clopidogrel was obtained as free base or the hydrogen sulfate salt. This invention further discloses a process for resolution of racemic clopidogrel and converting the (+)-clopidogrel base into its known polymorphs.

RX(2) OF 18





88%

CON: STAGE(1) 5 minutes, room temperature
STAGE(2) 1 hour, 25 deg C; 4 hours, reflux
STAGE(3) room temperature

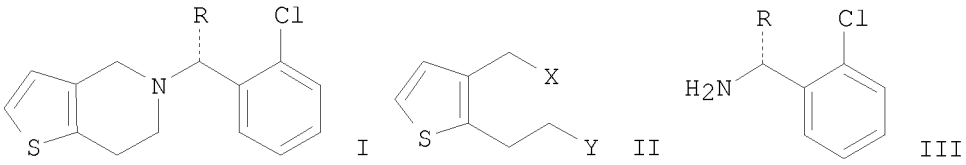
L6 ANSWER 23 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 143:326345 CASREACT
TITLE: preparation of chlorobenzylthienopyridines from chlorobenzylamines and hydroxymethylthiopheneethanol derivatives
INVENTOR(S): Yun, Sangmin; Kim, Eun Sook; Kim, Hee Seock; Ha, Tae Hee; Suh, Kwee-Hyun; Lee, Gwan Sun
PATENT ASSIGNEE(S): Hanmi Pharm. Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005087779	A1	20050922	WO 2005-KR586	20050303
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
KR 2005091330	A	20050915	KR 2004-16714	20040312
AU 2005222016	A1	20050922	AU 2005-222016	20050303
AU 2005222016	B2	20080214		
CA 2559571	A1	20050922	CA 2005-2559571	20050303

EP 1723149	A1	20061122	EP 2005-721898	20050303
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 1930172	A	20070314	CN 2005-80008059	20050303
BR 2005008597	A	20070821	BR 2005-8597	20050303
JP 2007528895	T	20071018	JP 2007-502702	20050303
RU 2322446	C1	20080420	RU 2006-136031	20050303
MX 2006PA10326	A	20061207	MX 2006-PA10326	20060911
US 20070197789	A1	20070823	US 2006-598790	20060912
IN 2006DN05824	A	20070831	IN 2006-DN5824	20061006
PRIORITY APPLN. INFO.:			KR 2004-16714	20040312
			WO 2005-KR586	20050303

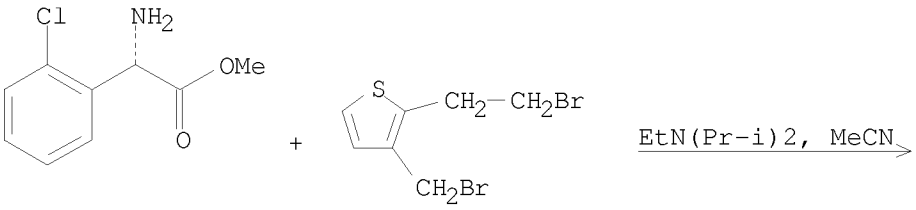
OTHER SOURCE(S): MARPAT 143:326345

GI

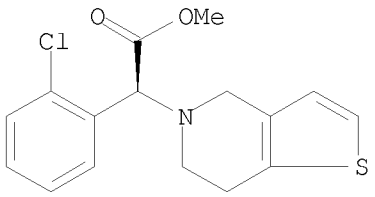


AB Title compds. (I; R = H, MeO2C), were prepared by reaction of thiophene derivs. (II; X, Y = Cl, Br, mesyloxy, tosyloxy) with chlorobenzylamines (III; R as above). Thus, 2-(2-bromoethyl)-3-bromomethylthiophene (preparation given), 2-chlorobenzylamine, and diisopropylamine were refluxed together for 5 h in MeCN to give 78% Ticlopidine.

RX(19) OF 109



HCl



88%

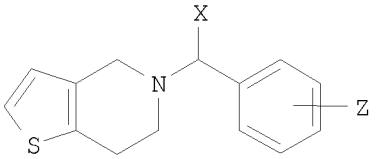
NOTE: tert-butanol can also be used as solvent, Et3N or K2CO3 can also be used as reagents
CON: STAGE(1) 0.5 hours, room temperature; 8 hours, reflux

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

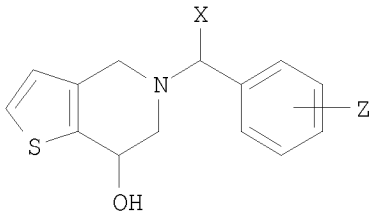
L6 ANSWER 24 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 143:78173 CASREACT
TITLE: Process for the preparation of tetrahydrothieno[3,2-c]pyridine derivatives
INVENTOR(S): Smyj, Robert P.; Weeratunga, Gamini
PATENT ASSIGNEE(S): Apotex Pharmachem Inc., Can.
SOURCE: U.S. Pat. Appl. Publ., 6 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050137401	A1	20050623	US 2004-774506	20040210
US 7060831	B2	20060613		
CA 2454015	A1	20050623	CA 2003-2454015	20031223
PRIORITY APPLN. INFO.:			CA 2003-2454015	20031223

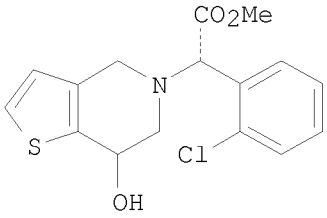
OTHER SOURCE(S): MARPAT 143:78173
GI



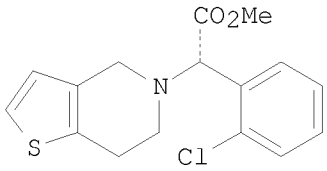
I



II



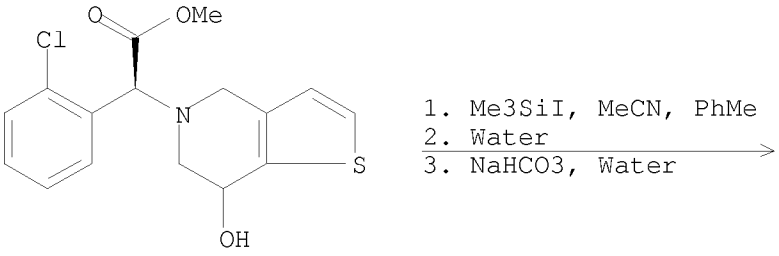
III



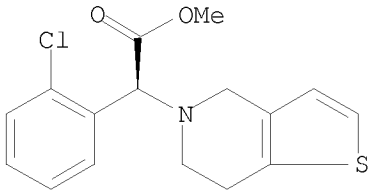
IV

AB A process for the preparation of tetrahydrothieno[3,2-c]pyridine I [X = carboxyl, alkoxycarbonyl, aryloxycarbonyl, or carbamoyl CONR1R2 (wherein R1 and R2 can be individually or simultaneously H, alkyl or part of a heterocyclic structure); Z = H, halo, alkyl, aryl, aryloxy or alkoxy] or their pharmaceutically acceptable salts, which comprises conducting a dehydroxylation of II in order to obtain a compound I, is disclosed. The said dehydroxylation reaction is effected by iodosilane Si(R4)3I (wherein R4 = alkyl, alkenyl, alkynyl, aryl, or combinations of thereof) which is generated in situ in the reaction between chlorosilane Si(R4)3Cl with NaI. Thus, treating NaI with TMSCl in MeCN followed by addition of (αS,7RS)-III in PhMe/MeCN afforded Clopidogrel free base (IV), known antithrombotic.

RX(1) OF 6



(step 1)



NOTE: in-situ generated reagent prior to addition of reactant in first stage
CON: STAGE(1) 0 - 5 deg C; 5 deg C -> room temperature; 2 hours, room temperature
STAGE(2) 0 - 5 deg C; 5 deg C -> room temperature; 4 hours, room temperature
STAGE(3) room temperature, basify

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

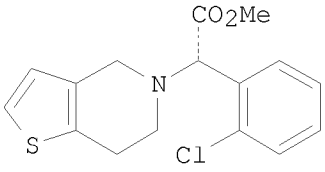
L6 ANSWER 25 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:316822 CASREACT
TITLE: Preparation of clopidogrel crystalline polymorphs for inhibiting platelet aggregation
INVENTOR(S): Arul, Ramakrishnan; Rawat, Ajay Singh; Gadakar, Maheshkumar; Rao, Rajesh; Pise, Abhinay; Gray, Jason
PATENT ASSIGNEE(S): Generics UK Limited, UK
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005026174	A1	20050324	WO 2004-GB3867	20040909

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

	EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004272337	A1	20050324	AU 2004-272337	20040909	
AU 2004272337	B2	20080214			
CA 2536052	A1	20050324	CA 2004-2536052	20040909	
EP 1618113	A1	20060125	EP 2004-768414	20040909	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR					
EP 1772456	A1	20070411	EP 2006-124851	20040909	
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
EP 1837337	A1	20070926	EP 2006-124847	20040909	
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
US 20070281964	A1	20071206	US 2007-571419	20070531	
AU 2008200919	A1	20080320	AU 2008-200919	20080227	
PRIORITY APPLN. INFO.:			GB 2003-21256	20030911	
			AU 2004-272337	20040909	
			EP 2004-768414	20040909	
			WO 2004-GB3867	20040909	

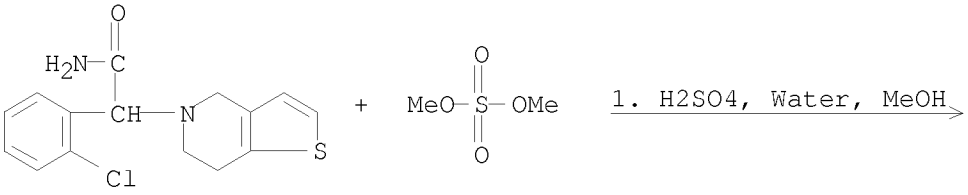
GI



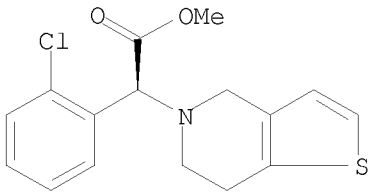
I

AB The present invention relates to novel crystalline forms of the platelet aggregation inhibitor (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate, clopidogrel (I), in the form of hydrogen bromide salts, identified as polymorph forms 1, 2 and 3. The present invention further relates to processes for preparing such forms, pharmaceutical compns. comprising such forms, and uses for such forms and compns. The pharmaceutical compns. may be used, in particular, for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina. The present invention also relates to methods of treating said disorders.

RX(5) OF 17



(step 2)



73%

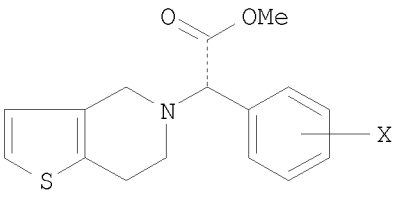
CON: STAGE(1) 25 - 38 deg C; 38 deg C -> reflux; 3 hours, reflux;
reflux -> 40 deg C
STAGE(2) 40 deg C -> 65 deg C; 60 hours, 65 - 66 deg C;
66 deg C -> 25 deg C

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:316818 CASREACT
TITLE: Process for the recovery of (S)-(+)-methyl (2-chlorophenyl)- (6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate (clopidogrel bisulfate) from its (R) and mixture of (R) and (S)-isomers
INVENTOR(S): Reddy, Manne Satyanarayana; Eswaraiah, Sajja; Reddy, Anumula Raghupathi; Sampath, Alla
PATENT ASSIGNEE(S): Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050059696	A1	20050317	US 2004-842702	20040510
IN 2003MA00389	A	20070727	IN 2003-MA389	20030508

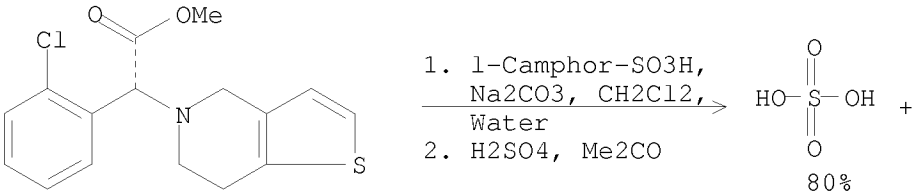
PRIORITY APPLN. INFO.: IN 2003-MA389 20030508
OTHER SOURCE(S): MARPAT 142:316818
GI



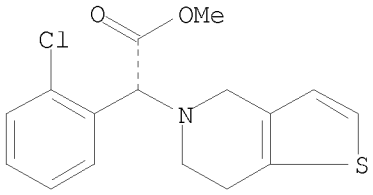
I

AB A process for the recovery of compound of formula (I) (where X = H, F, Cl, Br, iodo atom, preferably 2-chloro) which comprising the steps of (a) preparing compound (-)- or (±)-(2-chloro phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic acid Me ester hydrogen sulfate from its corresponding camphorsulfonic acid salt compound, (b) transforming the obtained compound of step (a), into the compound of (2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic acid, (c) converting the compound of step (b) into racemic compound (±)-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic acid Me ester hydrogen sulfate, (d) resolving the obtained racemic compound of step (c), into the optically active (+)-(2-chloro phenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic acid Me ester camphor sulfonic acid salt, and (e) further transforming the optically active (+) form compound of step (d) into their pharmaceutically acceptable salts.

RX(1) OF 6



(step 1)



80%

CON: STAGE(1) <60 deg C; 30 - 35 deg C; pH 7.5 - 8
STAGE(2) 20 - 25 deg C; 20 - 25 deg C; 1 hour, 20 - 25 deg C

L6 ANSWER 27 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:56276 CASREACT
TITLE: A process for preparation of clopidogrel via resolution of methyl α-[[2-(thien-2-yl)ethyl]amino]-α-(2-chlorophenyl)acetate, racemization of the undesired enantiomer, and cyclocondensation with formaldehyde

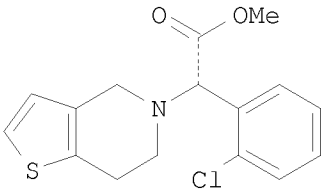
INVENTOR(S): Vaghela, Mukesh Nathalal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004108665	A2	20041216	WO 2004-IN106	20040419
WO 2004108665	A3	20050324		

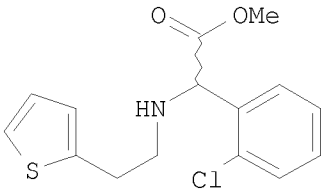
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN 2003MU00407	A	20050211	IN 2003-MU407	20030424

PRIORITY APPLN. INFO.: IN 2003-MU407 20030424
GI



I

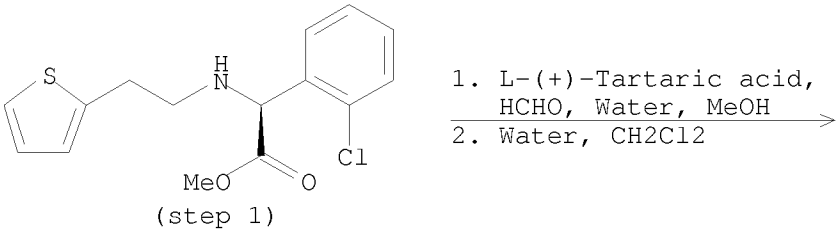


II

AB The invention provides an improved process for the preparation of the (S)-isomer of Me α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)-α-(2-chlorophenyl)acetate (I), or a salt thereof. I is the well-known antithrombotic and platelet aggregation inhibitor clopidogrel. The process comprises 4 steps: (a) resolving racemic Me α-[[2-(thien-2-yl)ethyl]amino]-α-(2-chlorophenyl)acetate (II) or a salt to obtain (S)-II or a salt and (R)-II or a salt; (b) racemizing (R)-II or a salt to obtain racemic II and optionally converting it into a salt; (c) optionally repeating steps a and b; and (d) converting (S)-II obtained in step a to I. The invention provides a simple process whereby unwanted isomers and derivs. that may be generated during resolution of II can be converted back to racemic II and recycled to produce the desired dextrorotatory isomer (S)-II, which is then converted to clopidogrel. Surprisingly, control of key parameters like concentration, agitation, and cooling during resolution provides the desired (S)-(+)-II tartrate salt in a single operation, directly from the reaction mixture, avoiding repetitive crystns. The other isomer (R)-II and derivs. of II remain in the mother liquor in the form of an enantiomerically enriched mixture, which can be

converted to racemic II, which can then be further recycled. In synthetic examples, DL-2-chlorophenylglycine Me ester was N-alkylated with 2-(2-thiophene)ethanol tosylate using NaHCO3 and KI in MeCN at 80° to give racemic II.HCl. This salt was neutralized with Na2CO3 between aqueous and CH2Cl2 layers, and the concentrated free base was resolved using (L)-(+)-tartaric acid (III) in iso-PrOH to give crystalline (S)-II.III with typical [αD] > +88°. The residue from the mother liquors containing (R)-II was racemized by sequential treatment with NaOMe in MeOH at 65-70°, followed by HCl in MeOH at 5-10°, a catalytic amount of DMF, and then SOCl2 at 5-15°, followed by warming to 30-35° and continued stirring. Workup and acidification gave crystalline racemic II.HCl. Meanwhile, (S)-II was freed from the above tartrate salt as the HCl salt, which was cyclocondensed with aqueous formaldehyde at 55° to give I free base. Treatment of I with H2SO4 in acetone gave clopidogrel bisulfate, [αD]=+56° (20°, c=1, MeOH).

RX(4) OF 10



(step 1)

CON: STAGE(1) 55 deg C; 3 - 4 hours, 55 deg C; 55 deg C -> 30 deg C

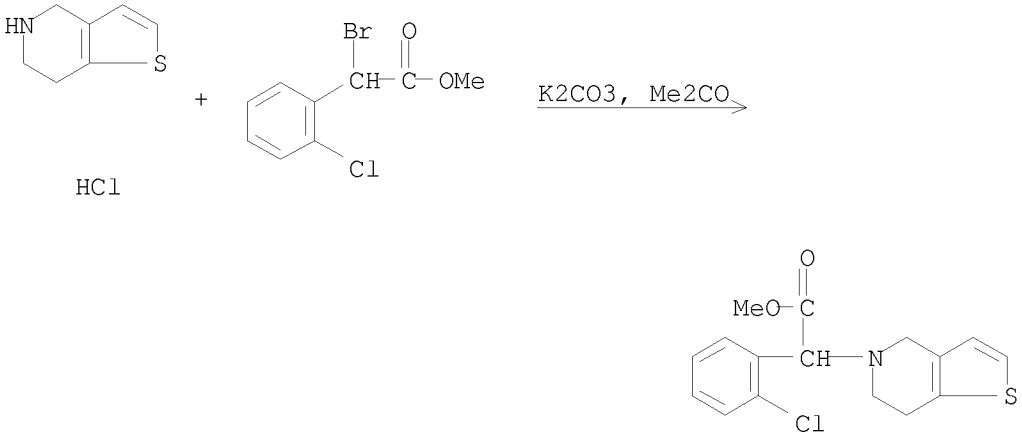
L6 ANSWER 28 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:146120 CASREACT
TITLE: Racemization and enantiomer separation of clopidogrel
INVENTOR(S): Valeriano, Merli; Daverio, Paola; Bianchi, Stefano
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries, Ltd., Italy
SOURCE: U.S. Pat. Appl. Publ., 11 pp., Cont.-in-part of U.S. Ser. No. 302,357.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040024012	A1	20040205	US 2003-392601	20030319
US 6800759	B2	20041005		
US 20040024011	A1	20040205	US 2002-302357	20021122
US 6737411	B2	20040518		
CA 2494528	A1	20040212	CA 2002-2494528	20021122

AU 2002350250	A1	20040223	AU 2002-350250	20021122
EP 1483269	A1	20041208	EP 2002-786781	20021122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 20050049275	A1	20050303	US 2004-958072	20041004
US 7259261	B2	20070821		
MX 2005PA01319	A	20050428	MX 2005-PA1319	20050201
IN 2005DN00431	A	20060721	IN 2005-DN431	20050204
PRIORITY APPLN. INFO.:			US 2002-400738P	20020802
			US 2002-302357	20021122
			WO 2002-US37680	20021122
			US 2003-392601	20030319

AB Processes for separation of enantiomers of clopidogrel, and converting one enantiomer of clopidogrel to another enantiomer of clopidogrel are provided. The enantiomers are separated by crystallizing the (S) enantiomer as camphor sulfonate salt from a hydrocarbon, or a mixture of a hydrocarbon and a co-solvent, preferably DMF:toluene. The (R) enantiomer is then racemized and recycled by reaction with a catalytic amount of a base, preferably with tert-butoxide. Thus, a solution of racemic clopidogrel in toluene was added to a solution of (R)-(-)-camphorsulfonic acid (CSA/Rac clopidogrel = 0.6/1 mol/mol) in DMF at 30°, seeded with (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-ylacetic acid Me ester-(-)-CSA salt (I), and then cooled to 15° to affect crystallization of the product. The product was filtered, washed with toluene, then dried under vacuum at ≤35°. After one crystallization of the salt I from acetone, it (90 g) was added to 462 mL EtOAc/H2O (60/40 volume ratio) and treated with 20 g 30% NaOH at .apprx.15° and adjusted to pH 8.1 with 9.2 g Na2CO3. The organic phase was separated, washed with water, decolorized with charcoal, filtered, concentrated in vacuo at room temperature and 30 mmHg, dissolved in 348 mL acetone, cooled to .apprx.15°, treated with 6.2 g 96% H2SO4, seeded with clopidogrel bisulfate, stirred for .apprx.7 h at 25°, filtered, and dried under vacuum to give 62.4 g (S)-(+)-chlorogrel bisulfate.

RX(2) OF 5



CON: room temperature

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

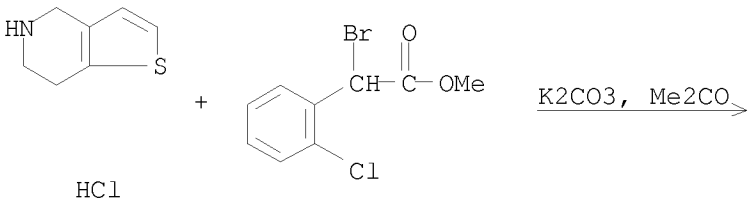
L6 ANSWER 29 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:146119 CASREACT

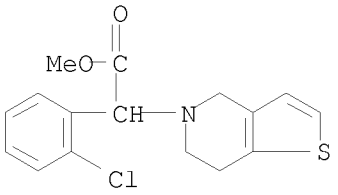
TITLE: Racemization and enantiomer separation of clopidogrel
INVENTOR(S): Valeriano, Merli; Daverio, Paola; Bianchi, Stefano
PATENT ASSIGNEE(S): TEVA Pharmaceutical Industries Ltd., Italy
SOURCE: U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040024011	A1	20040205	US 2002-302357	20021122
US 6737411	B2	20040518		
CA 2494528	A1	20040212	CA 2002-2494528	20021122
WO 2004013147	A1	20040212	WO 2002-US37680	20021122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002350250	A1	20040223	AU 2002-350250	20021122
EP 1483269	A1	20041208	EP 2002-786781	20021122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 20040024012	A1	20040205	US 2003-392601	20030319
US 6800759	B2	20041005		
US 20050049275	A1	20050303	US 2004-958072	20041004
US 7259261	B2	20070821		
MX 2005PA01319	A	20050428	MX 2005-PA1319	20050201
IN 2005DN00431	A	20060721	IN 2005-DN431	20050204
PRIORITY APPLN. INFO.:			US 2002-400738P	20020802
			US 2002-302357	20021122
			WO 2002-US37680	20021122
			US 2003-392601	20030319

AB Processes for separation of enantiomers of clopidogrel, and converting one enantiomer of clopidogrel to another enantiomer of clopidogrel are provided. The enantiomers are separated by crystallizing the (S) enantiomer as camphor sulfonate salt from a hydrocarbon, or a mixture of a hydrocarbon and a co-solvent, preferably DMF:toluene. The (R) enantiomer is then racemized and recycled by reaction with a catalytic amount of a base, preferably with tert-butoxide. Thus, a solution of racemic clopidogrel in toluene was added to a solution of (-)-(R)-camphorsulfonic acid (CSA/Rac clopidogrel = 0.6/1 mol/mol) in DMF at 30°, seeded with (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-ylacetic acid Me ester-(-) CSA salt (I), and then cooled to 15° to affect crystallization of the product. The product was filtered, washed with toluene, then dried under vacuum at ≤35°. After one crystallization of the salt I from acetone, it was added to EtOAc/H2O and treated with NaOH and Na2CO3. The organic phase was separated, washed with water, decolorized with charcoal, filtered, concentrated, dissolved in acetone, treated with H2SO4, seeded with clopidogrel polymorph seed, aged, filtered, and dried under vacuum at <25° to give chlorogrel bisulfate.

RX(2) OF 5





L6 ANSWER 30 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 139:364917 CASREACT
TITLE: A process for the preparation of clopidogrel
INVENTOR(S): Castaldi, Graziano; Barreca, Giuseppe; Bologna, Alberto
PATENT ASSIGNEE(S): Dinamite Dipharma S.p.A., Italy
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

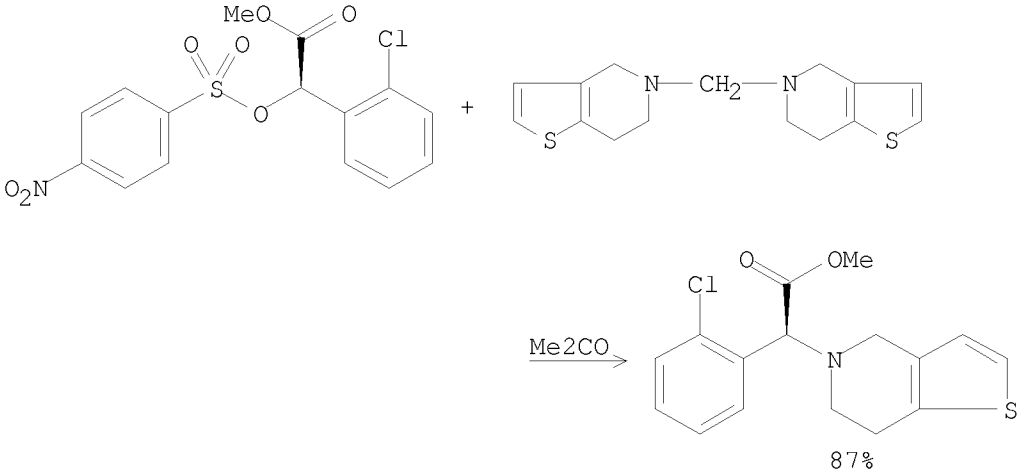
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093276	A1	20031113	WO 2003-EP4179	20030422
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IT 2002MI0933	A1	20031103	IT 2002-MI933	20020503
CA 2485070	A1	20031113	CA 2003-2485070	20030422
AU 2003224115	A1	20031117	AU 2003-224115	20030422
EP 1501838	A1	20050202	EP 2003-720514	20030422
EP 1501838	B1	20070411		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1649877	A	20050803	CN 2003-809967	20030422
JP 2005530757	T	20051013	JP 2004-501415	20030422
AT 359287	T	20070515	AT 2003-720514	20030422

ES 2285116	T3	20071116	ES 2003-720514	20030422
MX 2004PA10765	A	20050705	MX 2004-PA10765	20041029
HR 2004001017	B1	20070831	HR 2004-1017	20041029
US 20050143414	A1	20050630	US 2004-513156	20041102
US 7329751	B2	20080212		
PRIORITY APPLN. INFO.:			IT 2002-MI933	20020503
			WO 2003-EP4179	20030422

OTHER SOURCE(S): MARPAT 139:364917

AB A process for the preparation of clopidogrel by the condensation reaction of N,N'-bis(4,5,6,7-tetrahydro[3,2-c]thienopyridyl)methane with C1-4 alkyl (2R)-(2-chlorophenyl)-2-haloacetates or alkyl (2R)-2-(2-chlorophenyl)-2-(substituted sulfonyloxy)acetates [e.g., Me (2R)-2-(2-chlorophenyl)-2-(4-nitrobenzenesulfonyloxy)acetate].

RX(2) OF 7



NOTE: optimization study
CON: STAGE(1) 40 minutes, room temperature; 25 hours, room temperature

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 40 CASREACT COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 138:106680 CASREACT
TITLE: Process for the preparation of tetrahydrothieno[3,2-c]pyridine derivatives, particularly ticlopidine and clopidogrel, via novel intermediates
INVENTOR(S): Horne, Stephen E.; Weeratunga, Gamini; Comanita, Bogdan M.; Nagireddy, Jaipal Reddy; McConachie, Laura Kaye
PATENT ASSIGNEE(S): Brantford Chemicals Inc., Can.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004502	A1	20030116	WO 2002-CA1017	20020705

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2352520	A1	20030106	CA 2001-2352520	20010706
CA 2352520	C	20071002		
AU 2002317106	A1	20030121	AU 2002-317106	20020705
EP 1404681	A1	20040407	EP 2002-745008	20020705

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: CA 2001-2352520 20010706
WO 2002-CA1017 20020705

OTHER SOURCE(S): MARPAT 138:106680

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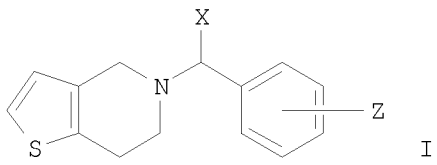

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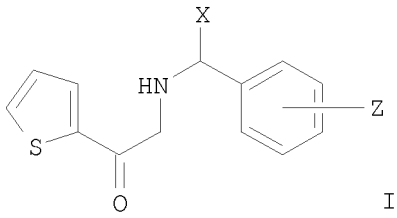

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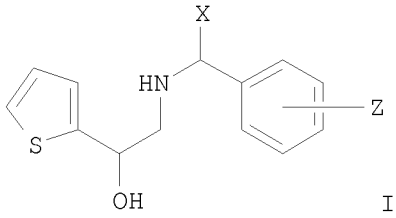

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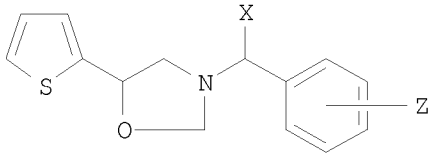
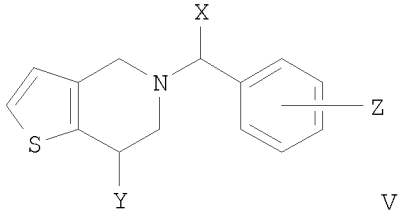


IV

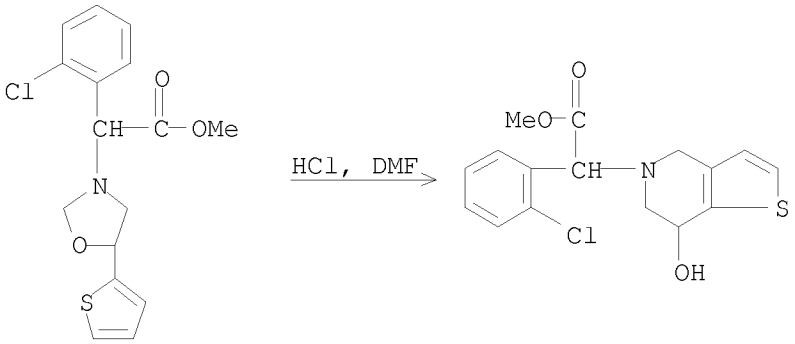


V

AB A process for the preparation of tetrahydrothieno[3,2-c]pyridine derivs. I and their pharmaceutically acceptable salts is disclosed [wherein: X = H, CO2H, alkoxycarbonyl, aryloxycarbonyl, nitrile, or CONR1R2; R1, R2 = H, alkyl, or part of a heterocycle; Z = H, halo, alkyl, aryl, aryloxy, or alkoxy]. Compds. I include the com. important drugs ticlopidine and clopidogrel, useful as antithrombotics and platelet aggregation inhibitors. The method comprising the steps of: (a) reduction of amino ketones II with suitable reducing agents to obtain amino alcs. III, (b) cyclization of III with formaldehyde (or any chemical equivalent) to obtain

oxazolidines IV, (c) rearrangement of IV to produce the (hydr)oxy-substituted tetrahydrothienopyridines V [Y = OH, alkanoyloxy, aroyloxy, carbamate or carbonate derivs.], and (d) reduction of V to give I. Synthetic examples are given for the preparation of racemic and (S)-isomeric clopidogrel. For instance, reaction of (S)-Me o-chlorophenylglycinate with 2-(bromoacetyl)thiophene in DMF at room temperature gave (S)-II (X = CO2Me, Z = o-Cl) with 95:5 enantiomeric ratio. Reduction of this ketone with NaBH4 in MeOH gave (S,RS)-III as a mixt of diastereomers. This alc. reacted with 37% formalin in EtOH at 40° to give, after evaporation and azeotropic distillation with PhMe, (S,RS)-IV. Rearrangement of the latter using HCl in dry DMF at 0-35° gave (S,RS)-V, which was reduced by SnCl2.2H2O and concentrated HCl in AcOH to give (S)-I (X = CO2Me, Z = o-Cl), i.e. clopidogrel, with a 98:2 enantiomer ratio. Racemic clopidogrel was prepared likewise. The method uses inexpensive reagents and gives good yields. The novel intermediates in the clopidogrel syntheses and their individual enantiomers are claimed per se.

RX(5) OF 30



NOTE: monitored to disappearance of starting material
CON: STAGE(1) 0 - 5 deg C; 0 deg C -> room temperature;
room temperature

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 32 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 138:24949 CASREACT
TITLE: Process for the preparation of tetrahydrothieno[3,2-c]pyridine derivatives
INVENTOR(S): Horne, Stephen E.; Weeratunga, Gamini; Comanita, Bogdan M.; Nagireddy, Jaipal Reddy; McConachie, Laura Kaye
PATENT ASSIGNEE(S): Brantford Chemicals Inc., Can.
SOURCE: U.S., 10 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6495691	B1	20021217	US 2001-902165	20010711

PRIORITY APPLN. INFO.: US 2001-902165 20010711
OTHER SOURCE(S): MARPAT 138:24949
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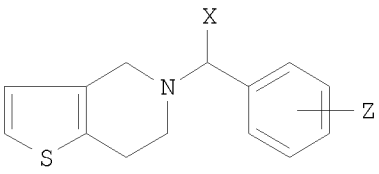
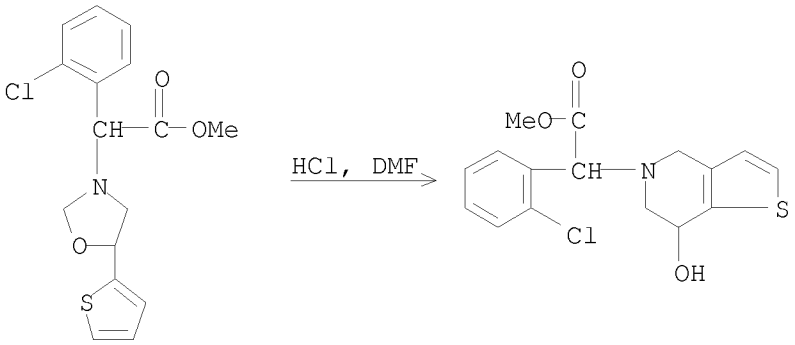


I

AB Tetrahydrothieno[3,2-c]pyridine derivs. I [X = carboxyl, alkoxycarbonyl, aryloxycarbonyl, or carbamoyl; Z = H, halo, alkyl, aryl, aryloxy, or alkoxy] or their pharmaceutically-acceptable salts were prepared from N-[2-(2-thienyl)-2-oxoethyl]-2-phenylglycinate derivs. Thus, treatment of 2-(bromoacetyl)thiophene with Me (o-chlorophenyl)glycinate in toluene-DMF in the presence of K2CO3 afforded Me N-[2-(2-thienyl)-2-oxoethyl]-2-(o-chlorophenyl)glycinate. The latter underwent borohydride reduction of the oxo group, cyclocondensation with formalin, treatment of the 1,3-oxazoline derivative with HCl in dry DMF, and dehydroxylation with HCl and SnCl2 in acetic acid to afford I (X = CO2Me, Z = 2-Cl).

RX(4) OF 15



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 137:140508 CASREACT
TITLE: Process for preparing clopidogrel and analogs via synthesis and/or resolution of corresponding acetamide and acetonitrile derivatives
INVENTOR(S): Pandey, Bipin; Lohray, Vidya Bhushan; Lohray, Braj Bhushan
PATENT ASSIGNEE(S): Cadila Healthcare Limited, India
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002059128	A2	20020801	WO 2002-IN12	20020121
WO 2002059128	A3	20021219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 191030	A1	20030913	IN 2001-MU84	20010124
US 20020177712	A1	20021128	US 2001-54101	20011022
US 6635763	B2	20031021		
CA 2436323	A1	20020801	CA 2002-2436323	20020121
AU 2002228325	A1	20020806	AU 2002-228325	20020121
AU 2002228325	B2	20060504		
EP 1353928	A2	20031022	EP 2002-710298	20020121
EP 1353928	B1	20061227		
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BR 2002007064	A	20040330	BR 2002-7064	20020121
JP 2004522744	T	20040729	JP 2002-559430	20020121
AT 349451	T	20070115	AT 2002-710298	20020121
ES 2278010	T3	20070801	ES 2002-710298	20020121
IN 194223	A1	20041002	IN 2003-MU23	20030108
IN 194222	A1	20041002	IN 2003-MU24	20030108
IN 194224	A1	20041002	IN 2003-MU26	20030108
IN 194221	A1	20041002	IN 2003-MU27	20030108
IN 194507	A1	20041113	IN 2003-MU25	20030108
IN 2003MU00402	A	20050211	IN 2003-MU402	20030422
IN 2003MU00403	A	20050211	IN 2003-MU403	20030422
NO 2003002898	A	20030903	NO 2003-2898	20030624
ZA 2003004895	A	20040512	ZA 2003-4895	20030624
MX 2003PA06133	A	20040504	MX 2003-PA6133	20030709
PRIORITY APPLN. INFO.:			IN 2001-MU84	20010124
			US 2001-54101	20011022
			US 2001-54120	20011022
			WO 2002-IN12	20020121

OTHER SOURCE(S): MARPAT 137:140508

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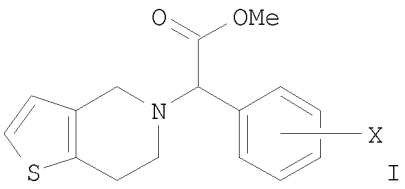

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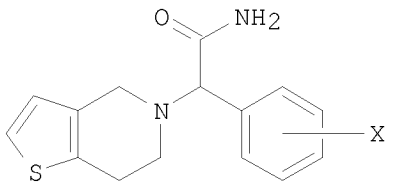

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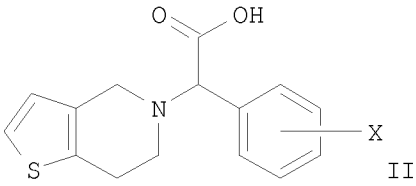
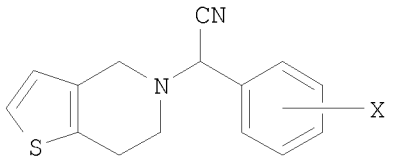


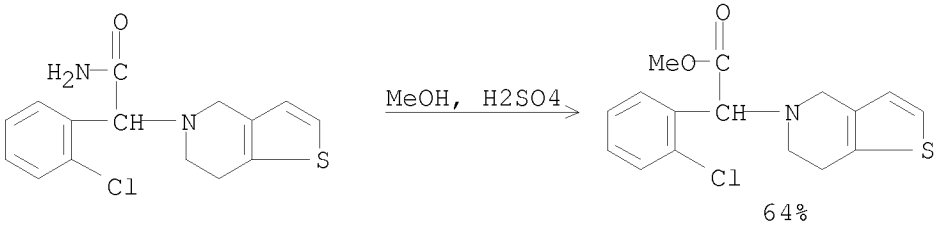
III



IV

AB The invention discloses a multi-step process for the preparation of thieno[3,2-c]pyridine Me ester derivs. of general formula I [X = H or halo], in either their racemic or optically active (+) or (-) forms, or their salts. The invention also describes processes for preparing the intermediate amides II, and further processes for preparing earlier intermediates, including the acids III and/or the nitriles IV. The compds. have one asym. carbon and hence, optically active I and II may be obtained either by resolving the racemic substance, or by using an optically active precursor, which may in turn be resolved. Processes for recycling undesired enantiomers by racemization are also disclosed. I include known, pharmacol. active substances, which have significant platelet anti-aggregating and anti-thrombotic properties. Particularly important is (S)-(+)-I (X = 2-Cl), which is the well-known drug clopidogrel. Thus, the invention aims to provide an inexpensive and com. viable process to prepare compds. I in good yields. A total of 55 synthetic examples are described in detail. For instance, condensation of o-chlorobenzaldehyde with NaCN and 6,7-dihydro-4H-thieno[3,2-c]pyridine in aqueous NaHSO3 gave 97% (±)-IV (X = 2-Cl). Treatment of this nitrile with KOH in t-BuOH gave 94% amide (±)-II (X = 2-Cl). Resolution of the racemic amide using (1S)-(+)-camphor-10-sulfonic acid gave the diastereomeric salt in 75% yield; this was hydrolyzed with aqueous base to give 64% (S)-(+)-II (X = 2-Cl). Alternatively, the diastereomeric amide salt was subjected directly to methanolysis with H2SO4 in refluxing MeOH to give (S)-(+)-I (X = 2-Cl), i.e. clopidogrel, in 97% yield. Treatment of the latter (clopidogrel base) with H2SO4 in acetone under controlled conditions gave polymorph I of clopidogrel bisulfate, m.p. 185° ± 1°, [αD] = +55.96°, and 99.85% ee.

RX(4) OF 46



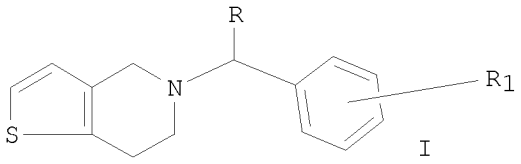
64%

NOTE: optimization study

L6 ANSWER 34 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 136:216655 CASREACT
TITLE: Preparation of acid addition salts of 4, 5, 6, 7 - tetrahydrothieno (3,2-c) pyridine derivatives having antithrombotic activity
INVENTOR(S): Tarur, Venkatasubramanian Radhakrishnan; Srivastava, Ranjan Prasad; Srivastava, Anita Rajan; Somani, Santosh Kumar
PATENT ASSIGNEE(S): Rpg Life Sciences Limited, India
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

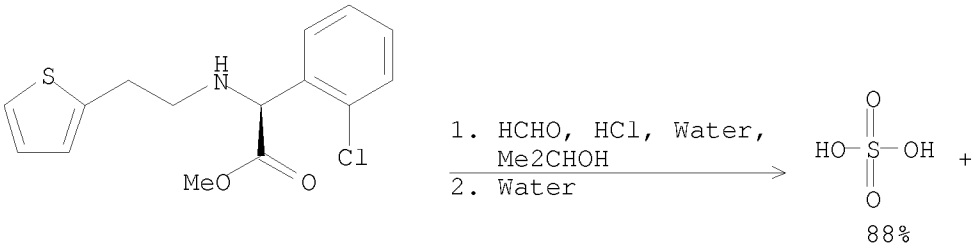
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018357	A1	20020307	WO 2000-IN80	20000829
WO 2002018357	A8	20020620		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001028789	A5	20020313	AU 2001-28789	20000829
PRIORITY APPLN. INFO.:			WO 2000-IN80	20000829

OTHER SOURCE(S): MARPAT 136:216655
GI

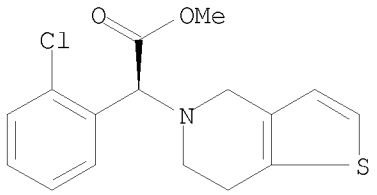


AB A one-pot preparation of pharmaceutically acceptable acid addition salts of 4,5,6,7-tetrahydrothieno(3,2-c) pyridine derivs. [I; wherein R = H or CO2R2 (R2 = (C1-C4)alkyl); R1 = (C1-C4)alkoxy, (C1-C4)alkoxy, (C1-C4)acyloxy, OH, NO2, or halo] is described. Thus, N-(2-chlorobenzyl)-2-(2-thienyl)ethylamine•HCl is refluxed with paraformaldehyde and HCl to give 90% 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno(2,3-c)pyridine. The prepared compds. are useful as antithrombotic agents (no data).

RX(2) OF 4



HCl
(step 1)



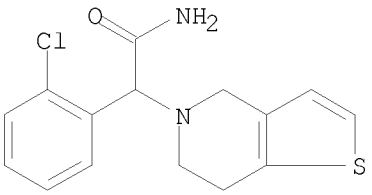
88%

NOTE: alternative prepn. gave lower yields, paraformaldehyde used

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

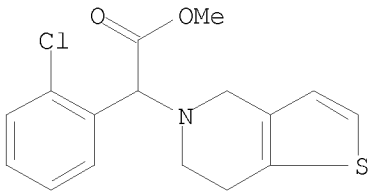
L6 ANSWER 35 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 133:281711 CASREACT
TITLE: ortho-metalation/chlorination of benzoic acid derivatives: preparation of [benzene-U-13C]-rac-clopidogrel ([benzene-U-13C]-rac-SR25990C)
AUTHOR(S): Burgos, Alain; Herbert, John M.; Simpson, Iain
CORPORATE SOURCE: Isotope Chemistry and Metabolite Synthesis Department, Sanofi-Synthelabo Research, Northumberland, NE66 2JH, UK
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2000), 43(9), 891-898
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Directed ortho-lithiation is used to form [benzene-U-13C]-2-chlorobenzaldehyde, the key building block for preparation of labeled racemic Clopidogrel [i.e., [benzene-U-13C]-rac-SR25990C; α-(2-chloro-13C-phenyl)-4,7-dihydrothieno[2,3-c]pyridine-6(5H)-acetic acid Me ester sulfate]. Some practical observations are reported concerning the metalation of some derivs. of benzoic acid.

RX(3) OF 17



(step 1)

1. MeOH, H2SO4
2. NaHCO3, Water, AcOEt
3. AcOEt
4. H2SO4, Et2O



50%

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 36 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 130:296510 CASREACT
TITLE: Hydroxyacetic ester derivatives, namely (R)-methyl 2-(sulfonyloxy)-2-(chlorophenyl)acetates, preparation method, and use as synthesis intermediates for clopidogrel
INVENTOR(S): Bousquet, Andre; Musolino, Andree
PATENT ASSIGNEE(S): SANOFI, Fr.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

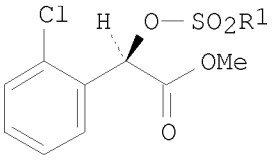
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918110	A1	19990415	WO 1998-FR2082	19980929
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
FR 2769313	A1	19990409	FR 1997-12441	19971006
FR 2769313	B1	20000421		
CA 2306409	A1	19990415	CA 1998-2306409	19980929
AU 9893544	A	19990427	AU 1998-93544	19980929
EP 1021449	A1	20000726	EP 1998-946523	19980929
EP 1021449	B1	20020102		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			

BR 9813022	A	20000815	BR 1998-13022	19980929
JP 2001519353	T	20011023	JP 2000-514920	19980929
JP 3827946	B2	20060927		
HU 2000004250	A2	20011028	HU 2000-4250	19980929
AT 211476	T	20020115	AT 1998-946523	19980929
PT 1021449	T	20020628	PT 1998-946523	19980929
ES 2171040	T3	20020816	ES 1998-946523	19980929
NO 2000001736	A	20000606	NO 2000-1736	20000404
NO 325150	B1	20080211		
MX 200003334	A	20001110	MX 2000-3334	20000405
US 6573381	B1	20030603	US 2000-509879	20001006
US 20030208077	A1	20031106	US 2003-425437	20030429
US 6894186	B2	20050517		
US 20040260110	A1	20041223	US 2004-890749	20040714
US 7153969	B2	20061226		
JP 2006124398	A	20060518	JP 2005-366868	20051220

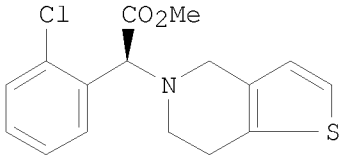
PRIORITY APPLN. INFO.: FR 1997-12441 19971006
JP 2000-514920 19980929
WO 1998-FR2082 19980929
US 2000-509879 20001006
US 2003-425437 20030429

OTHER SOURCE(S): MARPAT 130:296510

GI



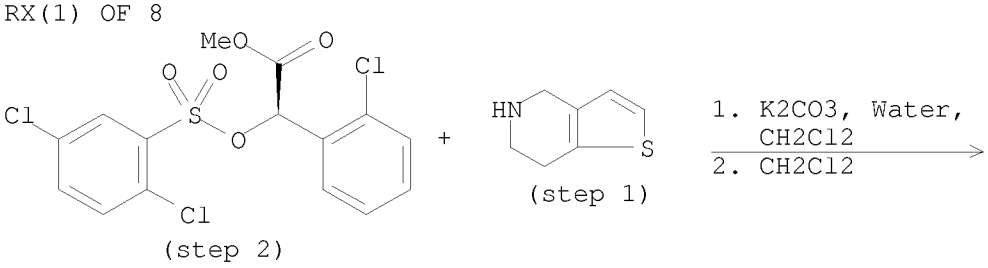
I



II

AB The invention concerns (R)-sulfonyloxyacetic ester derivs. of formula I [R1 = benzyl, C1-4 alkyl optionally substituted by one or several halogen atoms, or Ph optionally substituted by ≥1 halogen atoms, by ≥1 linear or branched C1-4 alkyl groups, or by nitro]. The compds. are intermediates in the synthesis of clopidogrel (II), a well-known antithrombotic and platelet antiaggregant. Several examples were prepared, and the compds. were employed in 2 different syntheses of II. For instance, (R)-2-hydroxy-2-(2-chlorophenyl)acetic acid was converted to its Me ester in 94% yield and >99% optical purity using H2SO4 in MeOH. The Me ester was treated with PhSO2Cl, pyridine, and LiClO4 in dichloroethane, to give title compound I [R1 = Ph] in 90% yield and >99% optical purity. Reaction of the latter with 4,5,6,7-tetrahydrothieno[3,2-c]pyridine in CH2Cl2 in the presence of aqueous 30% K2CO3 for 5 h gave II in 94.5% yield and 96.2% optical purity.

RX(1) OF 8



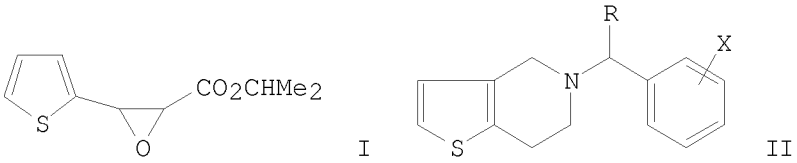
(step 2) (step 1)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 37 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 116:194139 CASREACT
TITLE: Isopropyl 2-thienylglycidate, process for its preparation, and its use as synthetic intermediate for ticlopidine and clopidogrel
INVENTOR(S): Bousquet, Andre; Calet, Serge; Heymes, Alain
PATENT ASSIGNEE(S): Sanofi SA, Fr.
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 465358	A1	19920108	EP 1991-401833	19910703
EP 465358	B1	19960207		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2664276	A1	19920110	FR 1990-8482	19900704
FR 2664276	B1	19921023		
US 5132435	A	19920721	US 1991-724988	19910702
CA 2046126	A1	19920105	CA 1991-2046126	19910703
CA 2046126	C	20011120		
JP 04261174	A	19920917	JP 1991-162859	19910703
JP 3055819	B2	20000626		
HU 61754	A2	19930301	HU 1991-2250	19910703
HU 213397	B	19970630		
AT 133950	T	19960215	AT 1991-401833	19910703
ES 2083542	T3	19960416	ES 1991-401833	19910703

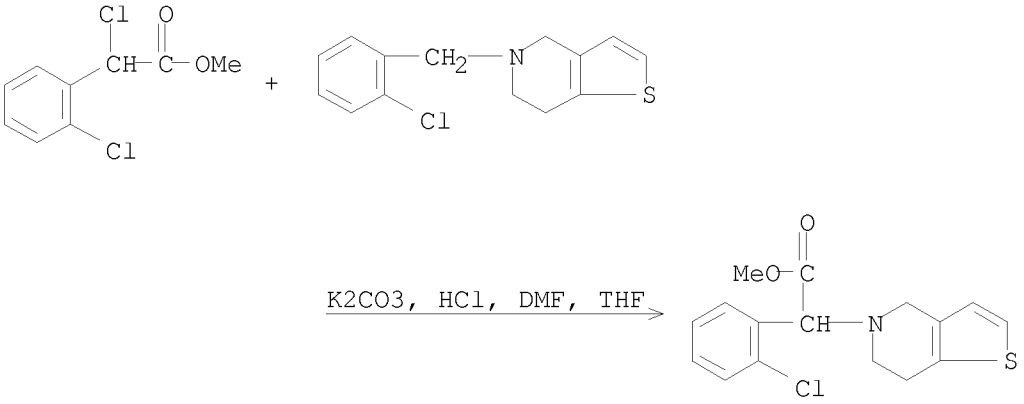
PRIORITY APPLN. INFO.: FR 1990-8482 19900704
OTHER SOURCE(S): MARPAT 116:194139
GI



I II

AB Title ester I, useful as an intermediate for antithrombotic/platelet antiaggregant thienopyridine derivs. II (R = H, CO2R1; R1 = C1-4 alkyl; X = H, halo), was prepared Thus, reaction of thiophene-2-carboxaldehyde with ClCH2CO2CHMe2 in Me2CHOH containing Me2CHONa at 20°, with workup and vacuum distillation, gave 93% I. Saponification of I and reaction with NH2OH.HCl (may also be performed in situ with preparation) gave 95% 2-thienylacetaldoxime, which underwent hydrogenation to the amine (91.5%), conversion to the formimine (100%), and cyclization (93%) to give 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-HCl. This underwent neutralization (100%) and benzylation with 2-ClC6H4CH2Cl (83%) to give ticlopidine-HCl, i.e. II-HCl (R = H, X = 2-Cl). Preparation of clopidogrel-H2SO4 is also described.

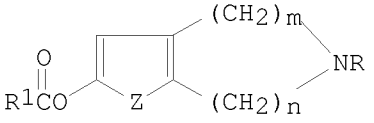
RX(8) OF 36



L6 ANSWER 38 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 115:183262 CASREACT
TITLE: Preparation of tetrahydrothienopyridines and analogs as elastase and platelet aggregation inhibitors
INVENTOR(S): Badorc, Alain; Bordes, Marie Francoise; Frehel, Daniel; Herbert, Jean Marc
PATENT ASSIGNEE(S): SANOFI, Fr.
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 421861	A1	19910410	EP 1990-402711	19901001
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2652579	A1	19910405	FR 1989-12854	19891002
FR 2652579	B1	19920124		
CA 2026386	A1	19910403	CA 1990-2026386	19900927
JP 03130289	A	19910604	JP 1990-264906	19901001
US 5190938	A	19930302	US 1990-591828	19901002

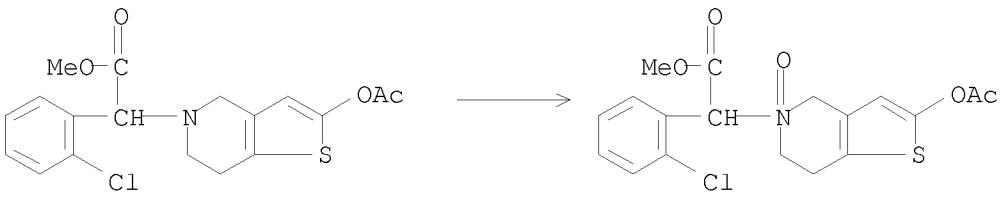
PRIORITY APPLN. INFO.: FR 1989-12854 19891002
OTHER SOURCE(S): MARPAT 115:183262
GI



I

AB The title compds. I [R3 = alkyl, Ph, benzyl; R = H, CHR2R5; R1 = R3, OR3; R2 = H, alkyl, CO2R4, etc.; R4 = H, alkyl, benzyl; R5 = H, alkyl, (substituted) Ph; Z = S, O; m, n = 1, 2], elastase inhibitors and platelet aggregation inhibitors useful in the treatment of inflammation, were prepared Treatment of 5-(2-chlorobenzyl)-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one with BuLi, followed by reaction with pivaloyl chloride, gave I (Z = S; m = 1; n = 2; R = CHR2R5; R2 = H; R5 = 2-ClC6H4; R1 = Me3C), which at 100 mg/kg gave 61% inhibition of ADP-induced platelet aggregation (animal species unspecified).

RX(7) OF 13



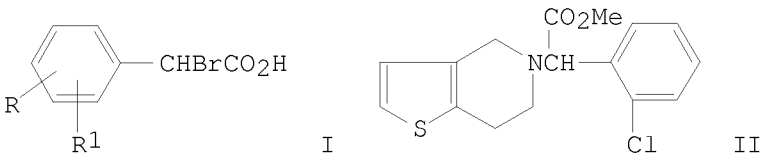
L6 ANSWER 39 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 115:114486 CASREACT
TITLE: Process for preparing phenylacetic derivatives of thienopyridines and intermediate α-bromophenylacetic acids
INVENTOR(S): Bouisset, Michel; Radisson, Joel
PATENT ASSIGNEE(S): SANOFI, Fr.
SOURCE: Eur. Pat. Appl., 7 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 420706	A2	19910403	EP 1990-401828	19900626

EP 420706	A3	19920304		
EP 420706	B1	19951011		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2652575	A1	19910405	FR 1989-12787	19890929
FR 2652575	B1	19920124		
AU 9057546	A	19910411	AU 1990-57546	19900618
AU 627590	B2	19920827		
CA 2019301	A1	19910329	CA 1990-2019301	19900619
CA 2019301	C	20000905		
NO 9002714	A	19910402	NO 1990-2714	19900619
US 5036156	A	19910730	US 1990-540483	19900619
ZA 9004830	A	19920226	ZA 1990-4830	19900621
JP 03120286	A	19910522	JP 1990-169672	19900626
JP 3176612	B2	20010618		
HU 55338	A2	19910528	HU 1990-3995	19900626
HU 207325	B	19930329		
DD 295851	A5	19911114	DD 1990-342102	19900626
SU 1836373	A3	19930823	SU 1990-4830875	19900626
AT 128961	T	19951015	AT 1990-401828	19900626
ES 2078956	T3	19960101	ES 1990-401828	19900626
US 5189170	A	19930223	US 1991-677482	19910329
LV 11683	B	19970820	LV 1996-268	19960718
PRIORITY APPLN. INFO.:			FR 1989-12787	19890929
			US 1990-540483	19900619

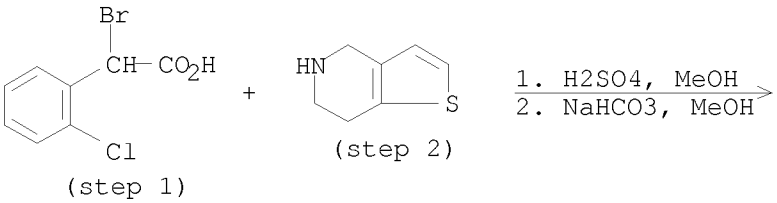
OTHER SOURCE(S): MARPAT 115:114486

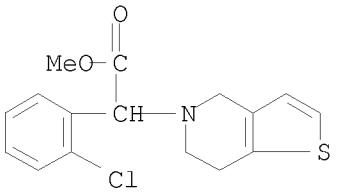
GI



AB Brommophenylacetic acids I (R, R1 = H, halogen) were prepared from RR1C6H3CHO and CHBr3 in the presence of KOH. Thus, 2-ClC6H4CHO was treated with CHBr3 and KOH in dioxane-ice to give 63% 2-ClC6H4CHBrCO2H which was converted to its Me ester and treated with 4,5,6,7-tetrahydrothieno[3,2-c]pyridine to give the thienopyridylacetate II.

RX(2) OF 3





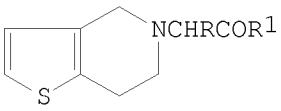
L6 ANSWER 40 OF 40 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 100:191856 CASREACT
TITLE: Thieno[3,2-c]pyridine derivatives and their therapeutical use
INVENTOR(S): Aubert, Daniel; Ferrand, Claude; Maffrand, Jean Pierre
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 99802	A1	19840201	EP 1983-401382	19830705
EP 99802	B1	19870204		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
FR 2530247	A1	19840120	FR 1982-12599	19820713
FR 2530247	B1	19860516		
IL 69049	A	19860331	IL 1983-69049	19830622
ZA 8304705	A	19840328	ZA 1983-4705	19830628
DK 8303041	A	19840114	DK 1983-3041	19830701
DK 157552	B	19900122		
DK 157552	C	19900611		
US 4529596	A	19850716	US 1983-510582	19830705
AT 25384	T	19870215	AT 1983-401382	19830705
AU 8316637	A	19840119	AU 1983-16637	19830707
AU 554358	B2	19860821		
ES 523943	A1	19840401	ES 1983-523943	19830707
CA 1194875	A1	19851008	CA 1983-432079	19830708
PL 142272	B1	19871031	PL 1983-242965	19830711
FI 8302543	A	19840114	FI 1983-2543	19830712
FI 73218	B	19870529		
FI 73218	C	19870910		
NO 8302530	A	19840116	NO 1983-2530	19830712
NO 159725	B	19881024		
NO 159725	C	19890201		

HU 31227	A2	19840428	HU 1983-2486	19830712
HU 187111	B	19851128		
DD 211351	A5	19840711	DD 1983-252993	19830712
CS 246062	B2	19861016	CS 1983-5281	19830712
SU 1272994	A3	19861123	SU 1983-3618709	19830712
JP 59027895	A	19840214	JP 1983-127519	19830713
JP 01000955	B	19890110		
CS 246082	B2	19861016	CS 1984-3815	19840521
PRIORITY APPLN. INFO.:			FR 1982-12599	19820713
			EP 1983-401382	19830705
			CS 1983-5281	19830712

OTHER SOURCE(S): MARPAT 100:191856

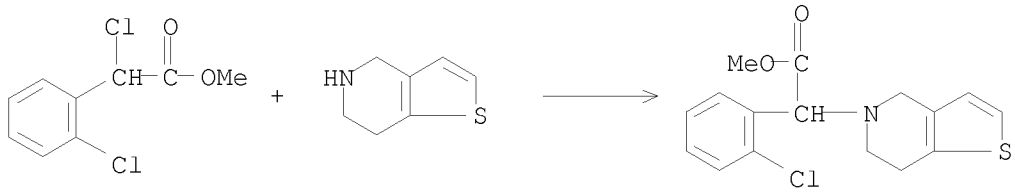
GI



I

AB Thienopyridines I (R = Ph, substituted Ph; R1 = OH, alkoxy, amino), useful as platelet aggregation inhibitors, were prepared Thus, I (R = 2-ClC6H4, R1 = OMe) was obtained in 45% yield by treating 4,5,6,7-tetrahydrothieno[3,2-c]pyridine with 2-ClC6H4CHClCO2Me. At 3 + 5 mg/kg orally in rats I (R = 2-ClC6H4, R1 = OMe) increased the bleeding time from 420 to 1080 s.

RX(1) OF 1



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